UNIVERSIDADE D
COIMBRA

Mariana Guerra da Cruz Diaz

Relatórios de estágio e Monografia intitulada "Update on Biosimilars – Quality, Regulatory Issues and Impact on the Public Healthcare" referentes a Unidade Curricular "Estágio", sob orientação da Dra. Diana Marques, da Dra. Cláudia Gama e da Professora Doutora Filipa Mascarenhas Melo, apresentados a Faculdade de Farmácia da Universidade de Coimbra, para apreciação na prestação de provas públicas de Mestrado Integrado em Ciências Farmacêuticas.

Setembro de 2022

FACULDADE DE FARMÁCIA
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Setembro 2022

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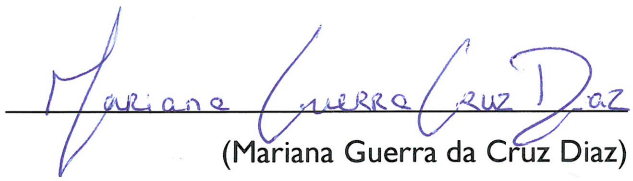

(Mariana Guerra da Cruz Diaz)

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A todos vocês, o meu mais sincero OBRIGADA!

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Capítulo I

Relatório de Estágio em Farmácia Comunitária

Farmácia Nogueira Janeiro

Sob a orientação da Dra. Diana Marques

I. Lista de Abreviaturas

EC	Estágio Curricular
FFUC	Faculdade de Farmácia da Universidade de Coimbra
FNJ	Farmácia Nogueira Janeiro
MICF	Mestrado Integrado em Ciências Farmacêuticas
MNSRM	Medicamentos Não Sujeitos a Receita Médica
SWOT	Strengths, Weakness, Opportunities, Threats

2. Introdução

Perante a sociedade em que vivemos, o farmacêutico desempenha um papel fundamental, uma vez que contribui para a promoção da saúde pública e manutenção da qualidade de vida, através da criação de laços de apoio e confiança com os cidadãos. As farmácias são um local de fácil acesso à saúde, onde o aconselhamento não tem qualquer custo associado, portanto, dada a situação económica que se vive em Portugal, as farmácias representam um elemento essencial. Assim sendo, é de a responsabilidade do farmacêutico ser rigoroso, responsável e dotado de elevadas competências técnicas, científicas e éticas, mantendo-se sempre atualizado, de forma a prestar os melhores serviços possíveis.

O Estágio Curricular (EC) em Farmácia Comunitária constitui uma das etapas finais do plano de estudos do Mestrado Integrado em Ciências Farmacêuticas (MICF), sendo um passo de extrema relevância para integrar e aplicar os conhecimentos teóricos conquistados ao longo de cinco anos, na Faculdade de Farmácia da Universidade de Coimbra (FFUC). Desta forma, o acompanhamento, formação e avaliação do estagiário ao longo do EC permite detetar qualquer desfasamento que se possa percecionar entre a realidade académica e o mercado de trabalho.

O meu EC foi realizado na Farmácia Nogueira Janeiro (FNJ), em Águeda, desde o dia 1 de abril ao dia 28 de julho de 2022. Fiquei sobre a orientação da Dra. Diana Marques, que me procurou sempre ajudar a evoluir em termos técnicos e científicos e, além disso, transmitiu-me toda a componente social e humana característica da profissão. A FNJ situa-se na Avenida Dr. Eugénio Ribeiro, um local privilegiado da cidade de Águeda, e encontra-se aberta de segunda-feira a sexta-feira, entre as 09h00 e as 20h00 e, ainda, aos sábados, das 9h00 às 13h00. A direção técnica encontra-se ao encargo da Dra. Margarida Brenha e a equipa técnica é composta por mais três farmacêuticos e três técnicos de farmácia.

O relatório apresenta-se sob a forma de uma análise SWOT (acrónimo das palavras inglesas *Strenghts, Weaknesses, Opportunities and Threats* (1), que permitirá fazer uma reflexão crítica e clara sobre a minha experiência, explorando ainda a integração da aprendizagem teórica e a adequação do MICF às perspetivas profissionais futuras.

3. Análise SWOT

3.1. Pontos Fortes

3.1.1. Localização da farmácia

A FNJ encontra-se situada na Avenida Dr. Eugénio Ribeiro (centro da cidade de Águeda), o que se revela uma mais-valia, na medida em que se trata de uma zona bastante movimentada, quer por pessoas mais idosas (principalmente, residentes de Águeda), quer pela população mais jovem (pois encontra-se ao lado de uma escola secundária e da Escola Superior de Tecnologia e Gestão de Águeda). Para além disso, nesta zona trabalha uma grande diversidade de pessoas (nomeadamente, em bancos, comércio, câmara municipal, padarias, entre outros), o que faz com que o público seja muito diversificado e com que haja também muitos clientes ocasionais, o que permite ao farmacêutico atuar sobre diferentes áreas terapêuticas. Desta forma, presenciei as mais distintas situações e casos, o que fez com que o meu ritmo de trabalho e a minha agilidade mental fosse aumentando.

3.1.2. Equipa Técnica

Um dos pontos fortes do meu EC na FNJ foi ter a oportunidade de conviver e aprender num ambiente saudável e bastante amigável, com uma equipa técnica jovem e dinâmica, cheia de boa disposição, paciência e calma e sempre pronta a ajudar-me. Esta equipa técnica tem como principal objetivo o bem-estar da população e a prestação de serviços de qualidade. Esta forma de estar reflete-se na fidelização de novos clientes e na manutenção de clientes habituais, pois estes sentem confiança e, sobretudo, amabilidade nos serviços prestados, uma vez que as relações não são meramente comerciais, mas sim quase de companheirismo. Além disso, as tarefas diárias estavam distribuídas previamente, de forma inteligente, otimizando a disponibilidade dos recursos humanos.

O bom e relaxado ambiente que me proporcionaram desde o primeiro dia de estágio, ajudou-me a ter o à-vontade suficiente para expor questões e dificuldades que me foram surgindo, contribuindo de forma bastante positiva para o meu processo de aprendizagem e adaptação – o que foi fundamental para o sucesso do estágio.

3.1.3. Ligação com outras farmácias

A FNJ faz parte de um grupo de três farmácias, geridas pelas mesmas pessoas, o que permite recorrer a transferências inter-farmácias de medicamentos que pudessem fazer falta,

quando as outras farmácias tivessem disponibilidade de *stocks*. Fazia parte das regras internas da farmácia, sempre que não houvesse um medicamento disponível, antes de pedir aos fornecedores, o primeiro passo era contactar as duas outras farmácias. Só se a resposta fosse negativa é que estava autorizada para fazer encomenda externa. Este ponto constitui uma mais-valia para os utentes deste grupo de farmácias, pois muitas das vezes não tinham de esperar que fossem os fornecedores a trazer o medicamento em falta, podiam simplesmente passar na outra farmácia para o levantar ou então pedir para que fosse enviado para a farmácia em questão.

3.1.4. *Robot*

O *robot* é uma ferramenta que contribui para o bom funcionamento da FNJ, pois permite uma melhor gestão de *stocks* e datas de validade dos medicamentos. Este mecanismo armazena os medicamentos de acordo com o seu tamanho, registando a respetiva data de validade (de forma automática ou manual), consoante a existência ou não de um código QR na embalagem. Assim, é possível manter a informação sobre as necessidades de medicamentos otimizada, para além de haver uma melhor gestão das validades dos medicamentos. Para além disso, facilita a dispensa dos medicamentos por parte do farmacêutico, minimizando erros e maximizando o tempo de atendimento. Desta forma, a atenção está mais concentrada nas necessidades de cada utente.

3.1.5. Formações

Durante o meu EC na FNJ tive a oportunidade de realizar diversas formações, tanto de medicamentos não sujeitos a receita médica (MNSRM), como de produtos de dermocosmética e de suplementos alimentares, que contribuíram fortemente para o enriquecimento da minha aprendizagem e, consequentemente, para um maior grau de confiança da minha parte no aconselhamento ao utente. Estas formações foram facultadas por delegados de informação médica e formadores de diferentes laboratórios farmacêuticos e cosméticos, que frequentemente se deslocavam à farmácia com o intuito de nos apresentar e esclarecer acerca dos produtos que representam. Para além destas formações, tive também acesso a várias plataformas *online*, onde era possível fazer formações creditadas e não creditadas, pela Ordem dos Farmacêuticos.

Todas estas pequenas aprendizagens contribuíram para a minha formação enquanto futura farmacêutica, elucidando-me para as inúmeras aplicações e restrições de certos

produtos de saúde, assim como me estimularam e capacitaram para a execução de vendas cruzadas (*cross-selling*), proporcionando uma melhoria no atendimento ao cliente e alertando-me para diferentes oportunidades de negócio.

3.2. Pontos Fracos

3.2.1. Medicamentos Manipulados

A FNJ não tem a possibilidade de produzir Medicamentos Manipulados, o que constitui um dos únicos pontos fracos do meu EC, uma vez que não tive a possibilidade de contactar com esta realidade.

3.2.2. Erros de stock

Na FNJ existe um *stock* (número de embalagens disponíveis na farmácia) para todos os produtos disponíveis para venda, que pode ser consultado através do Sifarma®. O que acontecia muitas vezes era que o *stock* estava errado, o que me causava constrangimento e atrapalhação ao nível do atendimento, pois tinha de justificar ao utente o porquê de lhe ter dito que havia um produto que afinal não há. Além disso, estes erros eram sinónimo de mais trabalho de *backoffice* para toda a equipa, inclusive para mim, pois tínhamos de confirmar o stock do respetivo produto e acertar no sistema informático.

3.3. Oportunidades

3.3.1. Estágio extracurricular

Durante o verão de 2020 realizei um estágio extracurricular numa outra farmácia, por isso foi mais fácil o período inicial de familiarização com as práticas da farmácia comunitária. Apesar de aí apenas ter tido acesso ao Sifarma® 2000, senti que me foi útil, uma vez que, neste novo estágio, todos os assuntos relacionados com gestão e receção de encomendas, entre outros, eram realizados no Sifarma® 2000. Além disso, nesse estágio extracurricular, embora que sempre com supervisão, tive a possibilidade de contactar com as várias facetas de um farmacêutico, fazendo com que as possíveis dificuldades iniciais no EC fossem minimizadas.

3.3.2. VALORMED

A VALORMED surgiu em 1999 e é uma sociedade sem fins lucrativos, que criou um sistema de gestão para resíduos de embalagens vazias e de medicamentos não usados, contribuindo para a preservação do meio ambiente e para a proteção da saúde pública (2). Na

minha opinião, esta iniciativa constitui uma oportunidade para as farmácias, pois contribuiu para uma maior consciencialização do farmacêutico e dos utentes para a responsabilidade ambiental e social.

3.4. Ameaças

3.4.1. Desvalorização, por parte da sociedade, do papel do farmacêutico comunitário

Uma das principais ameaças à carreira de Farmacêutico Comunitário é, na minha opinião, a desvalorização da profissão por parte da sociedade. Ao longo deste EC, infelizmente, percecionei várias situações em que o farmacêutico não é tratado como um profissional de saúde, mas sim como um mero vendedor de caixas de medicamentos. Por conseguinte, e do meu ponto de vista, o farmacêutico deve sempre que possível mostrar os seus conhecimentos e mostrar que é fulcral para a sociedade em que vivemos. Está nas mãos do farmacêutico a sua própria valorização.

3.4.2. Ceticismo em relação aos medicamentos genéricos

Ao longo deste período em FC, fui-me apercebendo da desconfiança que muitos utentes ainda têm relativamente aos medicamentos genéricos. Durante os atendimentos ao balcão, ouvi diversas vezes dizerem que "só o de marca é que faz bem", ideia muito frequentemente associada ao facto de os genéricos serem mais baratos. Acho de extrema importância o farmacêutico, aquando destas intervenções, explicar ao utente o que são na realidade os medicamentos genéricos e desmistificar as crenças a eles associadas.

3.4.3. Cursos técnicos de farmácia

Uma outra ameaça que, na minha opinião, tem vindo cada vez a ser mais notória para os estudantes de MICF é a existência do curso técnico de Farmácia. Ao longo deste curso, os estudantes têm acesso a um elevado número de estágios, o que faz com que a sua componente prática seja muito forte. Além disso, o salário destes profissionais é mais baixo do que o dos farmacêuticos, o que, dada a situação económica e financeira que afeta o nosso país, é mais interessante para a entidade patronal.

3.4.4. Plano curricular de MICF e aconselhamento

Apesar de o plano curricular do MICF contemplar uma unidade curricular de Dermofarmácia e Cosmética e outra de Preparações de Uso Veterinário, senti uma maior dificuldade nestas duas áreas no que toca ao aconselhamento. No que toca à Dermofarmácia e Cosmética, considero que apenas foi feita uma abordagem superficial dos possíveis aconselhamentos, o que constituiu uma limitação ao meu desempenho no atendimento. Ao nível da veterinária, não tivemos preparação suficiente para a realidade do dia-a-dia. Para além disso, os conhecimentos relativos aos suplementos alimentares também são escassos, dada a pouca preparação que temos ao longo do curso. Isto tudo fez com que tivesse de recorrer, frequentemente, às minhas colegas, a fim de esclarecer dúvidas.

4. Casos Práticos

Durante o meu EC na FNJ foram inúmeras as oportunidades de realizar aconselhamento farmacêutico e de colocar em prática os conhecimentos adquiridos, tanto no plano curricular do MICF como das formações que me foram permitidas assistir. Nesta parte do relatório encontram-se cinco casos práticos que se destacaram dos demais.

Caso Prático I

Uma jovem adulta deslocou-se à FNJ com uma prescrição médica com indicação para dispensa de Fosfomicina 3g, 1 saqueta. Este fármaco pertence à classe de antibióticos de largo espetro e é frequentemente utilizado na prevenção e tratamento de infeções das vias urinárias baixas. Inicialmente, questionei a utente se esta teria alguma hipersensibilidade ao antibiótico, ao que ela me respondeu que não se lembrava de tal, mas que achava que não. Depois expliquei-lhe que um dos principais efeitos secundários deste medicamento é a diarreia, que causa perda de líquidos e desconforto. Portanto, aconselhei-lhe um complexo com prebióticos e probióticos, a fim de promover o equilíbrio da flora intestinal, e a ingestão de água, que, para além de promover a hidratação, promove também a eliminação das bactérias. Por último, informei ainda a utente de que o conteúdo da saqueta deve ser dissolvido num copo de água e tomado de uma só vez, para além de que deve ser tomado uma hora antes das refeições (ou duas horas depois), pois alguns alimentos diminuem a absorção da fosfomicina.

Caso Prático II

Uma mulher de 35 anos dirigiu-se até à farmácia e queixou-se de hemorroidas, com dor e ardor sempre que vai à casa de banho. Como se tratava de uma situação muito precoce, optei por aconselhar o Faktu®, um dispositivo médico indicado para distúrbios hemorroidais pois atua, principalmente, através da proteção da mucosa. Além disso, referi também a importância de não comer comidas picantes e de lavar a zona com água morna, a fim de diminuir a inflamação e, consequentemente, o ardor, através da vasoconstrição.

Caso Prático III

Um homem, com cerca de 40 anos, dirigiu-se à FNJ e solicitou "Griponal®". Perguntei ao utente quais os sintomas que tinha, ao que ele respondeu "nariz entupido" e "dores de cabeça", e acrescentou que febre não tinha. Portanto, não havendo mais nenhum sintoma, conclui tratar-se de uma constipação e aconselhei proceder à lavagem nasal com água do mar (aliviando o congestionamento nasal) e à toma de Paracetamol 500 mg (para o alívio das dores de cabeça). Além disso, relembrei ainda da importância da ingestão de água, por tratar-se de uma situação autolimitada. O utente perguntou-me então se, caso não melhorasse, poderia intercalar a toma de Paracetamol com "Griponal®", ao que lhe respondi que não e expliquei que o Griponal® já contém na sua composição paracetamol, na dosagem de 500 mg, e que a toma conjunta poderia acarretar uma dose excessiva dessa substância. Referi ainda que os sintomas, à partida, iam melhorar com as indicações sugeridas, mas que se isso não acontecesse nos próximos sete dias, para consultar um médico.

Caso Prático IV

Uma mulher, com cerca de 30 anos, dirigiu-se à farmácia e explicou que o filho, de 18 anos, ia fazer um exame e, por tal, estava muito ansioso, o que já lhe tinha gerado diarreia. Perguntei há quanto tempo estava assim e se havia algum outro sintoma, como febre, ao que me respondeu que apenas tinha começado naquela manhã e que não tinha febre. Portanto, expliquei à utente que era importante o seu filho ingerir muitos líquidos e aconselhei a toma de Imodium Rapid® (comprimidos orodispersíveis, contendo 2 mg de loperamida), para parar a diarreia. Além disso, aconselhei também um medicamento homeopático, Sedativ PC®, para o alívio da ansiedade (dois comprimidos para chupar, três vezes por dia). Por fim, alertei para

o facto de que se os sintomas de diarreia continuassem por mais dois dias, ou então se surgissem outros sintomas, como febre ou vómitos, o indicado era ir ao hospital.

Caso Prático V

Uma rapariga de cerca de 20 anos dirigiu-se à farmácia e pediu-me a pílula do dia seguinte. Fiz-lhe algumas questões, nomeadamente se a pílula em questão era para ela própria e se, assim sendo, tomava outro contracetivo. Disse-me que tomava a pílula Denille® - trata-se de uma pílula combinada, de toma oral, composta por um estrogénio (etinilestradiol) e por uma progesterona (dienogest). Acrescentou ainda que se tinha esquecido de tomar os dois primeiros comprimidos da cartela e que tinha tido relações sexuais desprotegidas há menos de 48 horas. Por conseguinte, aconselhei-lhe a Postinor (1,5 mg de levonogestrel), toma única, e alertei-a para o facto de que se vomitasse nas 3 horas seguintes teria de repetir a toma. Além disso, expliquei-lhe que existem outros métodos contracetivos, como o anel vaginal, que são melhores opções para quando o esquecimento da toma da pílula oral é comum, e que, portanto, deveria consultar um ginecologista, a fim de perceber quais as opções existentes e qual melhor se adequa à sua situação.

5. Conclusão

Estes 4 meses de EC na FNJ foram o culminar de um processo de aprendizagem e desenvolvimento profissional e pessoal relativo ao MICF, onde tive a oportunidade de pôr em prática alguns dos conhecimentos adquiridos ao longo do curso. Na minha opinião, o MICF ficaria incompleto se não existisse a experiência do EC, uma vez que somente nesta etapa conseguimos aliar o conhecimento académico e teórico à prática profissional.

Com esta experiência tive a oportunidade de contactar diretamente com as várias atividades inerentes à prática farmacêutica, que me fizeram perceber que o trabalho do farmacêutico vai muito além daquilo a que, tradicionalmente, se associa ao seu papel. O farmacêutico comunitário é insubstituível na sociedade atual, visto que, para além de ser o especialista do medicamento, é um verdadeiro agente de saúde pública. Foi-me possível constatar a confiança que os utentes depositam no farmacêutico e nos serviços da farmácia, sendo que, é importante referir que, muitas das vezes, o farmacêutico é o primeiro profissional de saúde a quem o utente recorre. Portanto, é exigida uma enorme responsabilidade, competência e constante atualização de conhecimentos.

Não posso concluir sem deixar uma palavra de grande apreço à equipa da FNJ que, durante estes quatro meses, me acolheu calorosamente e me prestou o melhor auxílio e a melhor colaboração possíveis. Foram incansáveis na transmissão de conhecimento, o que me permitiu crescer enquanto profissional de saúde.

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Capítulo II

Relatório de Estágio em Indústria Farmacêutica

Bluepharma Indústria Farmacêutica S.A.

Sob a orientação da Dra. Cláudia Gama

1. Lista de Abreviaturas

CQ	Controlo de Qualidade
EC	Estágio Curricular
FFUC	Faculdade de Farmácia da Universidade de Coimbra
GMPs	Good Manufacturing Practices
HPLC	Cromatografia Líquida de Alto Desempenho
IF	Indústria Farmacêutica
MIA	Métodos Instrumentais de Análise
MICF	Mestrado Integrado em Ciências Farmacêuticas
QA	Química Analítica
TF	Tecnologia Farmacêutica

2. Introdução

O Mestrado Integrado em Ciências Farmacêuticas (MICF) é um curso universitário que permite aos alunos seguirem diversas vertentes profissionais relacionadas com o ciclo do medicamento, nomeadamente farmácia comunitária, farmácia hospital, análises clínicas, indústria farmacêutica, entre outras. Então, de forma a expandir o meu conhecimento, ter uma nova experiência profissional e uma melhor perceção das saídas do MICF, decidi realizar também um estágio em indústria farmacêutica (IF). Desta forma, iniciei o meu estágio curricular (EC) no dia 10 de janeiro de 2022, na Bluepharma Pharmaceutical Industry, S.A. (Bluepharma), sendo que este teve fim a 30 de março de 2022. Este estágio teve como principal objetivo proporcionar um contacto mais sério com aquilo que é o mercado de trabalho, nomeadamente o mundo da indústria farmacêutico, constituindo um momento de conexão entre a vida académica e a vida profissional. Para além disso, serviu também como complemento a tudo o que aprendi ao longo dos cinco anos de MICF, permitindo-me demonstrar todo o meu conhecimento, potencial e capacidade de trabalho.

A minha jornada na Bluepharma® passou pelo departamento de Controlo de Qualidade (CQ), mais concretamente Validação de Limpeza, sobre a orientação da Dra. Claúdia Gama. O departamento de Controlo de Qualidade, como um todo, é responsável por analisar as matérias-primas, verificando assim a sua identidade e pureza, analisar produtos semiacabados, embalagens e folhetos informativos. Cabe também a este setor a implementação de métodos e a realização de testes piloto. Ou seja, o seu principal objetivo é garantir que os produtos farmacêuticos cumpram os parâmetros exigidos.

Este relatório tem a estrutura de análise SWOT, que permite fazer uma abordagem estruturada de todas as experiências vividas no decorrer deste EC (1).

3. Bluepharma

A Bluepharma® é uma IF portuguesa, com sede em Coimbra, que iniciou a sua atividade no mês de fevereiro de 2001, após a compra das instalações da Bayer (multinacional na área do medicamento de origem alemã) (2).

Esta IF dedica-se à investigação, desenvolvimento, fabrico e comercialização do medicamento. Produz formas farmacêuticas sólidas não-estéreis para uso oral, nomeadamente cápsulas e comprimidos, e tem autorização para fabricar produtos de investigação medicinal, supositórios, semissólidos e líquidos (2,3).

Apesar de ser uma empresa muito jovem, conta já com diversos marcos honrosos, de entre os quais podemos destacar as diversas certificações quer a nível da qualidade (ISO

9001/2000 em 2003), ambiental (ISO 14001/1999 em 2003), segurança e saúde ocupacional (OHSAS 18000 em 2003) e mais recentemente certificação em Investigação, Desenvolvimento e Inovação (IDI). Em 2009, passou ainda a ser portadora da autorização da FDS para produção e desenvolvimento de fórmulas sólidas (2–4).

O departamento de CQ é composto pelo Laboratório Físico-químico e pelo Laboratório de Microbiologia. É neste departamento que se realizam análises com recurso a métodos farmacopeicos e protocolos internos, recorrendo a tecnologia de análise de ponta, com o objetivo de garantir e monitorizar os padrões de qualidade dos produtos fabricados e comercializados pela Bluepharma® (5).

A Bluepharma® tem apostado muito fortemente na contratação de jovens, que são liderados por profissionais com vários anos de experiência, o quer gera um grande espírito de equipa e, portanto, condições de trabalho ideais.

4. Validação de Limpeza

O processo de validação de limpeza é cada vez mais um assunto do dia-a-dia na indústria farmacêutica, sendo que se tornou um dos requerimentos das GMPs (*Good Manufacturing Practices*). Este processo tem como finalidade provar que os níveis de substância ativa, microrganismos e detergentes presentes após a limpeza do equipamento são adequados, e é exigido para todos os equipamentos que estiveram em contacto com o produto durante a sua produção (6,7).

Normalmente, este processo apenas é necessário para equipamentos que sejam usados na produção de produtos diferentes. No caso de equipamentos que apenas produzem um único produto, só é necessário realizar esta validação para contaminantes que possam afetar a qualidade do produto produzido (detergentes e/ou microrganismos), e apenas é preciso validar os *holding times* de sujo (tempo decorrente entre o uso do equipamento e a sua limpeza) e de limpo (tempo decorrente entre a limpeza do equipamento e a sua utilização) (6).

A amostragem pode ser feita diretamente (por *swabs*), indiretamente (por enxaguamento), ou através de placas para avaliação microbiológica. Durante o estágio, tive o privilégio de várias vezes me dirigir à produção e assistir e ajudar no processo de recolha de amostras, de forma direta, através de *swabs* (7).

Em suma, para garantir a validação do processo de limpeza, é necessário assegurar que existe um procedimento de limpeza por cada equipamento que esteja em contacto com o produto durante a sua produção e um método de ensaio adequado e sensível, a fim de identificar níveis residuais (7). Para além disso, é preciso que haja um limite residual real que

demonstre que o equipamento está efetivamente limpo. Por último, é essencial a existência de um protocolo que assegure que a validação foi bem-sucedida, que seja assinado e aprovado por técnicos especialistas de diversas áreas (6,7).

5. Análise SWOT

5.1. Pontos Fortes

5.1.1. Processo de seleção

A seleção dos alunos que irão estagiar na Bluepharma® é feita através da avaliação do *Curriculum Vitae* e de uma entrevista, contrariamente ao que acontece nos outros locais onde também é possível realizar EC (hospitais, farmácias, outras empresas). Do meu ponto de vista, este é um aspeto bastante importante, pois permite que tenhamos um primeiro contacto com a realidade do mercado de trabalho.

5.1.2. Uso de diversos equipamentos

Ao longo do EC na Bluepharma® tive a oportunidade de manusear diferentes equipamentos e aprender as técnicas a eles associadas. Nestes equipamentos estão incluídos os equipamentos de HPLC (Cromatografia Líquida de Alto Desempenho), que é uma técnica amplamente utilizada na análise de separação, identificação e quantificação de compostos ativos de uma determinada amostra. Na faculdade, já tinha tido a oportunidade de aprender os conceitos básicos do processo, porém foi aqui que aprendi mais sobre a manipulação do *software* (que difere de acordo com o modelo – *Waters* ou *Shimadzu*) e a escolha de componentes do sistema cromatográfico (detector, colunas e fases móveis). Desta forma, acompenhei o uso do equipamento para a determinação de impurezas nas amostras coletadas após a limpeza das máquinas (processo de validação de limpeza), bem como, mais esporadicamente, para a determinação do conteúdo e impurezas do produto semiacabado.

Além dos equipamentos de HPLC, tive também a oportunidade de trabalhar, diariamente, com balanças, que são instrumentos fundamentais para alcançar reprodutibilidade nos resultados. Isto revelou-se interessante, pois estas balanças funcionam de forma distinta daquela a que fomos habituados no MICF, uma vez que é necessário que tudo o que seja pesado esteja registado, portanto têm de ter acoplado um registador.

Além destes dois, tive ainda um breve contacto com equipamentos como *Particle Size* (para detecção do tamanho das partículas na formulação), espectrofotómetros, aparelhos de dissolução, aparelhos de desagregação, entre outros.

5.1.3. Colheita de amostragens na produção

Ao longo do EC, tive a oportunidade de me dirigir inúmeras vezes à secção de produção da Bluepharma®, uma vez que era necessário colher as amostras, para posterior validação de limpeza da máquina em questão. Na minha opinião, isto foi um aspeto bastante positivo, uma vez que me permitiu contactar com outra realidade que não o laboratório. Pude visualizar as diferentes máquinas de produção e de embalamento, o que foi muito interessante para rever alguns conhecimentos adquiridos em Tecnologia Farmacêutica (TF) e Métodos Instrumentais de Análise (MIA). Além disso, pude contactar com outros profissionais e perceber o papel do farmacêutico nessa mesma secção.

5.1.4. Relações interpessoais, fácil integração e bom ambiente

Um dos grandes pontos fortes do EC foram as relações interpessoais. O facto de conhecer diversas pessoas, cada uma com a sua maneira de ser e com o seu percurso profissional, é importante para ir aprendendo novas coisas e me tornar mais completa e polivalente. A pandemia da COVID-19 trouxe muita solidão e aprendemos cada vez mais a trabalhar no nosso espaço, sozinhos, e ter a oportunidade de conviver diretamente com os meus colegas de trabalho foi gratificante.

Para além disso, para conseguir tirar todo o proveito do EC é necessário que exista uma boa integração desde o início. Quando cheguei à Bluepharma fui logo muito bem recebida pelos Recursos Humanos. Depois, fui encaminhada para a analista Sara Margarida (técnica analista de CQ), que me apresentou aos restantes funcionários do departamento e me fez uma breve visita ao laboratório de CQ. Depois, fui apresentada à minha colega de equipa, a analista Andreia Vieira, que me guiou e me ensinou durante todo o período de estágio. Inicialmente, foi ela quem me explicou como o laboratório estava organizado, onde estavam os reagentes, materiais de proteção pessoal, material de laboratório, equipamentos e amostras. Além disso, também me explicou todas as políticas, processos e objetivos do trabalho.

Desta forma, tive o enorme privilégio de trabalhar numa equipa jovem, multidisciplinar, altamente experiente e com espírito de entreajuda, que me orientou e respondeu a todas as dúvidas da melhor forma possível, o que contribuiu para o sucesso do meu estágio. Para além disso, é de realçar toda a disponibilidade e simpatia demonstradas, que fizeram com que me sentisse bastante à vontade, facilitando a minha integração.

5.1.5. Autonomia

O facto de me terem dado alguma autonomia na realização de certas tarefas, nomeadamente, determinação do teor em água, desagregação, divisibilidade, uniformidade de massa, uniformidade de dose unitária quantificada por espectroscopia UV/visível, preparação de fases móveis, solventes e tampão, contribuiu para que encarasse os problemas e os tentasse solucionar, estimulando, assim, o meu espírito crítico e de aprendizagem.

5.1.6. Formação contínua

Durante o EC, proporcionaram-me diversas formações internas, em diferentes áreas, o que foi fundamental para o meu sucesso e para a correta execução das tarefas, pois permitiram-me alargar os meus conhecimentos e desenvolver novas habilidades.

Inicialmente, participei em formações de acolhimento, cujo objetivo foi dar conhecimento da evolução histórica da empresa, da sua política de Recursos Humanos e do Sistema de Gestão Integrada. Depois, tive formações ao nível da farmacovigilância, da rede interna (*Outlook*, *Cisco Jaber* e *Helpdesk*), de outras ferramentas informáticas necessárias no trabalho, dos perigos que existem na internet, de alguns conceitos básicos de Assuntos Regulamentares, de Validação Analítica e outra que abordava como lidar com os *Outliers*. A nível prático, tive uma formação de "Boas Práticas de Pesagem" e outra relativa a "Pesagem em Cabines de Contenção", que me permitiram ganhar mais autonomia ao longo do EC.

5.2. Pontos Fracos

5.2.1. Rentabilidade do tempo

Ao longo do EC na Bluepharma® fui tendo diversos momentos em que não me era atribuída qualquer atividade. A área de Validação de Limpeza é uma área em que, por norma, não há muito para fazer e, portanto, na minha opinião, uma pessoa sozinha consegue lidar com o trabalho. Diversas vezes no laboratório estava só a observar, o que não foi estimulante. Além disso, quando a minha colega estava de volta da documentação relativa às análises laboratoriais, eu apenas ficava a observar. Aconteceu também que, nesses dias em que seria tratamento de documentação, eu era encaminhada para auxiliar outra colega da área de análise do produto semi-acabado, o que se revelou uma mais-valia para mim. No entanto, não posso deixar de apontar como ponto fraco esta má gestão do tempo.

5.3. Oportunidades

5.3.1. Conteúdo teórico e prático do MICF

Ao longo dos cinco anos de MICF, em unidades como TF, MIA e Química Analítica (QA), fui adquirindo competências técnicas e laboratoriais, nomeadamente através do contacto com diversos equipamentos e com as técnicas a eles associadas, que me facilitaram a integração nas atividades realizadas no EC. Notei que possuía alguma agilidade no uso de materiais de laboratório, bem como na elaboração de soluções, realização de diluições, medição de volumes e pesagem de amostras. Desta forma, transmiti confiança à minha companheira de equipa, Andreia, que me deu a oportunidade de realizar certas tarefas de forma independente, com o devido rigor.

5.3.2. Aprofundamento de conhecimentos

Durante o EC foi possível aprofundar alguns conhecimentos que já possuía, bem como aprender novos conceitos e novas formas de abordar e resolver problemas, o que contribuiu para melhorar aquilo que é a atitude e o espírito crítico que um profissional da IF deve possuir. Para além disso, como se tratava de um trabalho muito minucioso, desenvolvi a capacidade de ser o mais meticulosa possível, de forma a obter os melhores resultados possíveis.

5.3.3. Percepção do papel do farmacêutico na indústria farmacêutica

Embora não tao visível para a opinião pública, o farmacêutico exerce um grande papel na IF, e este EC permitiu-me percecionar isso mesmo – o que ainda não tinha conseguido fazer ao longo do plano de estudos de MICF. Este período em que estive na Bluepharma® foi importante para adquirir algumas noções sobre o que é trabalhar numa empresa deste ramo, nomeadamente a dinâmica empresarial, a organização dos diversos departamentos e a forma como tudo se articula, para que o resultado seja um produto de excelência.

5.4. Ameaças

5.4.1. Outros técnicos analistas

Durante este EC, fiquei ciente de que existem algumas ameaças à carreira de farmacêutico neste setor, tanto para indivíduos que já trabalham na área, quanto para aqueles que, como eu, estão a entrar pela primeira vez. Isto porque, apesar de ser uma área dedicada aos farmacêuticos, cada vez mais profissionais têm ganho espaço na IF, o que torna o mercado

mais competitivo. Acho extremamente importante haver uma maior afirmação por parte do farmacêutico, dado este ser o verdadeiro "especialista do medicamento".

5.4.2. Duração do estágio

O EC em IF tem a duração máxima de três meses, pois só assim é possível de conciliar com o EC em Farmácia Comunitária, que é de cariz obrigatório. Na minha opinião, trata-se de um período curto e que acaba por limitar o estagiário. Este estágio tem muitos conceitos novos e requer uma integração por parte do estudante, e o que acontece é que quando realmente começamos a realizar mais tarefas e a ser mais autónomos, o estágio acaba, revelando-se então um ponto fraco a ter em conta.

6. Conclusão

O meu estágio na Bluepharma® permitiu adaptar-me a uma nova realidade, o que foi fundamental, principalmente para ganhar maturidade, e proporcionou-me a oportunidade de adquirir novas competências essenciais para o meu futuro profissional, tais como o rigor necessário ao cumprimento de normas e tarefas e a responsabilidade no tratamento de documentação regulamentar. Consegui com este estágio compreender como funciona a IF, desde o processo de investigação e desenvolvimento do medicamento até à sua comercialização.

Posso dizer que a FFUC me forneceu todas as bases para que esta experiência fosse a mais positiva possível, sendo que as cadeiras de MIA, TF e QA foram essenciais. Contudo, considero que o plano curricular de MICF ficaria a ganhar com a inclusão de disciplinas (opcionais), que estivessem mais relacionadas com o mundo da indústria farmacêutica.

Olhando para a análise SWOT apresentada anteriormente, é fácil perceber que o que sobressaiu ao longo deste EC foram os pontos fortes e as oportunidades.

Concluindo, este EC revelou-se um acréscimo para a minha vida profissional e pessoal e, por isso, quero deixar o meu agradecimento a toda a equipa da Bluepharma®, especialmente aos membros do departamento de CQ, por todo o conhecimento, disponibilidade e apoio prestados.

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Capítulo III

Monografia

"Update on Biosimilars – Quality, Regulatory Issues and Impact on the Public Healthcare"

Sob a orientação do Professora Doutora Filipa Mascarenhas Melo

1. List of Abbreviations

ADAs	Anti-drug Antibodies
AEs	Adverse Events
APFH	Portuguese Association of Hospital Pharmacists
BD	Biodisponibility
CHMP	Committee for Medicinal Products for Human Use
CNFT	Pharmacy and Therapeutics National Commission
CQAs	Critical Quality Attributes
EEE	European Economic Area
EMA	European Medicine Administration
EU	European Union
Fab	Fragment antigen-binding
Fc	Fragment crystallizable
FcγR	Fragment crystallizable-gamma Receptor
FcRn	Neonatal Fragment Crystallizable Receptor
FDA	Food and Drug Administration
FIMEA	Finnish Medicines Agency
G-CSF	Granulocyte Colony-Stimulating Factor
GH	Growth hormone
ICH	International Conference of Harmonization
INFα	Interferon alpha
INFβ	Interferon beta
INN	International Naming System
MA	Marketing Authorization
mAb	Monoclonal Antibody
NHS	National Health Service

PD	Pharmacodynamics
PK	Pharmacokinetic
PTMs	Post Translational Modifications
PV	Pharmacovigilance
QbD	Quality-by-Design
QTPP	Quality Target Product Profile
RP	Reference Product
SmPC	Summary of Product Characteristics
tRNA	Transfer RNA
WHO	World Health Organization

Resumo

As terapêuticas biológicas vieram transformar os tratamentos de inúmeras doenças. As patentes e exclusividade dos medicamentos biológicos estão a expirar, o que criou uma oportunidade para o desenvolvimento e aprovação dos biossimilares – produtos com perfis de segurança, qualidade e eficácia semelhantes aos produtos de referência já aprovados.

Os biossimilares não são equivalentes genéricos aos biológicos de referência: são cópias não idênticas, semelhantes aos produtos de referência. São desenvolvidos e avaliados usando um rigoroso processo, passo-a-passo, que envolve avaliações analíticas, funcionais, não clínicas e ensaios clínicos. Os estudos clínicos para biossimilares são diferentes daqueles usados para o produto de referência aprovado, uma vez que o seu objetivo é mostrar que são semelhantes em termos de eficácia, segurança e imunogenicidade, e não demonstrar benefício clínico *per se*. No entanto, embora o conhecimento atual sobre biossimilares tenha aumentado significativamente, ainda existem várias controvérsias e equívocos sobre conceitos como imunogenicidade, extrapolação, *interchangeability*, substituição e nomenclatura.

O desenvolvimento de biossimilares veio estimular a competição no mercado, contribuir para a sustentabilidade da saúde e garantir um maior acesso dos doentes às terapias biológicas. Porém, para haver uma maximização dos benefícios dos biossimilares é necessário que haja cooperação entre os agentes reguladores e os responsáveis pelo seu desenvolvimento, a fim de garantir que o alcance aos doentes é rápido e não compromete os padrões de qualidade, segurança e eficácia. Além disso, é essencial que haja uma total compreensão do utente em relação aos biossimilares, para prevenir os efeitos placebo e, assim, haver sucesso no tratamento.

Esta monografia visa explicar os aspetos regulamentares dos biossimilares, quais os requerimentos de fabricação e quais as informações médicas necessárias para prescrever os biossimilares corretamente.

Palavras-chave: Biossimilares, Desenvolvimento, *Interchangeability*, Comissão Nacional de Farmácia e Terapêutica, Estudos de qualidade, Conceitos regulamentares.

Abstract

Biologic therapies have transformed high-burden treatments. Patent and exclusivity biological medicines are expiring, creating an opportunity for the development and approval of biosimilars – products with similar safety, quality, and efficacy profiles to previously licensed reference products.

Biosimilars are not generic equivalents to the originator: they are non-identical copies, similar reference products. They are developed and evaluated using a rigorous step-by-step process that involves analytical, functional, nonclinical evaluations, and clinical trials. Clinical studies for biosimilars are different from those used for the approved reference product because their purpose is to justify similar efficacy, safety, and immunogenicity, and not to demonstrate clinical benefit *per se*. However, although current knowledge regarding biosimilars has increased significantly, several controversies and misconceptions still exist regarding immunogenicity, extrapolation, interchangeability, substitution, and nomenclature.

The development of biosimilars stimulates market competition, contributes toward healthcare sustainability, and allows for greater patient access. However, maximizing biosimilar benefits involves cooperation between regulators and developers to guarantee that they reach patients rapidly without compromising quality, safety, or efficacy standards. Also, patient understanding regarding biosimilars is essential for treatment success and to prevent nocebo effects.

This review aims to explain biosimilar regulatory, manufacturing demands and what medical information is needed to prescribe biosimilars correctly.

Keywords: Biosimilars, Development, Interchangeability, Pharmacy and Therapeutics National Commission, Quality studies, Regulatory.

2. Introduction

In 1980, biological medicines emerged and began to be developed as a new group of medicines produced in living systems, using biotechnological methods (recombinant DNA technology), which differentiates them from traditional chemical synthesis medicines. These differences led to the need for specific legislation adapted to these new medicines (1–4).

Since then, biological medicines have shown their value as a key health technology in life-threatening diseases (cancer, multiple sclerosis, rheumatoid arthritis, diabetes and autoimmune diseases), being one of the most promising segments of the pharmaceutical industry, with several million patients benefiting from their use. With the fall of their patents, biosimilars appeared as equivalent alternatives. However, to gain their place in the market, they needed to demonstrate an equal safety profile as their reference biologicals (4–6).

This review article aims to explain the differences between biological medicines and biosimilars, and between these and intended copies, biobetters, and standalone biologics. We will also emphasize the development and regulatory aspects necessary for the approval of biosimilars, through a detailed explanation of the demonstration of analytical similarity, and non-clinical and clinical biosimilarity. In addition, it also focuses on how the safety control of biosimilars is carried out post-marketing (pharmacovigilance) and on the disputes concerning these medicines that still exist (immunogenicity, extrapolation, interchangeability and substitution, and nomenclature). Finally, an example model of implementation of biosimilars in a hospital context is also described, referring to the relevant economic aspects, and the position of the Portuguese Association of Hospital Pharmacists (APFH) and the Pharmacy and Therapeutics National Commission (CNFT) recommendations.

3. Biological medicines

The human body continually produces enzymes, hormones, antibodies, and other endogenous substances necessary for its survival. The aim of science has always been to imitate this ability. More than two decades ago, in 1999, biological medicines were introduced on the market (7). They are produced from living cells, using biotechnology techniques, unlike common medicines, which are produced from chemical synthesis in the laboratory (8–10). Nowadays, biological medicines are essential in the treatment of a variety of diseases, such as rheumatoid arthritis, cancer, multiple sclerosis, and other autoimmune diseases (7,10).

Biological medicines are much more complex and bigger than small-molecules drugs (4). Currently, they are divided into three main categories: (1) products almost identical to endogenous factors, often used as replacement therapy; (2) monoclonal antibodies (mAbs) that bind to soluble or cell surface targets, blocking cell signaling pathways and their functional responses; (3) engineered proteins that mimic receptors (soluble receptors, receptor antagonists, fusion proteins) (4). More specifically, biological medicines are produced as hormones (as is the case of insulin, for hormone deficiencies, and growth hormone, for growth hormone disorders), mAb (e.g., for the treatment of autoimmune diseases and cancer), blood products (e.g. for the treatment of hemophilia), immunomodulators (e.g. interferon beta, for multiple sclerosis), enzymes (e.g. for the removal of blood clots) and vaccines for the prevention of various diseases (11,12).

The production of most biological drugs is done through genetically modified host cells, which can be derived from plants, yeasts, bacteria, or animals. Each manufacturer has its own host cell bank, allowing it to produce a unique cell line. Furthermore, each manufacturer develops its own manufacturing process (11). First, the genetic code of the chosen protein is identified, which can be a hormone, an antibody, or a blood derivative, among others, and then a functional DNA sequence is generated. This genetic code is inserted into various host cell lines (e.g., yeast or bacteria) for them to produce this protein. Then, the strain that produces the most effective protein is selected and cultivated in bioreactors, a process called fermentation. Afterwards, outside the bioreactor, the protein is separated, purified, stabilized, and processed into a drug (13).

The problem with biological drugs lies in that their activity can be impaired by environmental and manufacturing conditions, making it difficult to achieve equivalent purity between different batches (4). Several factors contribute to this: inadequate selection of the cell line; biophysical characteristics of proteins; changes in temperature or pH conditions during the cultivation phases; handling and conservation of the product in the various stages

of manufacture; drug product formulation; production scale; production site. In other words, this process is so complex that there are manufacturers who haven't touched their cell lines for years, so as not to run the risk of altering the conditions under which the drugs are being made (4,12).

In recent years, patents, and other periods of exclusivity, of numerous biological medicines have expired. This has led to the development and approval of "biosimilars", products that are alike the already licensed biologicals (4,10,12,14).

3.1. Biosimilars

In the guideline issued by the European Medicine Agency (EMA), it is mentioned that a biosimilar is highly similar to another biological drug already approved in the European Union (EU) (reference product – RP) in terms of quality characteristics, biological activity, safety, and efficacy (according to the EMA, a biosimilar is a biological medicine that possesses highly similar quality characteristics, biological activity, safety, and efficacy to a biological medicine already approved in the European Union (EU) (RP)) (15). The biosimilar's pharmacokinetic (PK) and pharmacodynamic (PD) properties are similar to those of an existing biological medicine (i.e., a medicine that has already been approved by EMA and is used in the EU, according to approved therapeutic indications) (16). When the approved biological medicine is no longer protected by its exclusivity period (generally 10 years) or by patent, a biosimilar medicine can be introduced on the market (4,10,14,17,18).

Knowing that complexity and heterogeneity are inherent characteristics of all biological medicines (not limited to biosimilars), it is easy to see that biosimilars are not intrinsically more variable than reference products (RPs) and the existing variability has no impact on their efficacy and safety (10,19).

It is relevant to clarify that a biosimilar is not a generic medicine in the definition of the generic term – the differences are presented in Annex A (14,17). While both are "variants" of already approved branded drugs, the terms "biosimilar" and "generic" are not interchangeable (20). Generics are chemically synthesized small molecules, which makes them chemically identical to RP. In contrast, biosimilars are produced by a living cell, and although two living cells may have the same amino acid sequence for a protein, natural changes in glycosylation or protein folding can occur. In other words, generating a biological medicine equal to RP is impossible, however, it is possible to generate a highly similar molecule, in terms of quality, biological and clinical activity, safety, and efficacy (4,17,20,21).

Assessing the comparability of quality attributes (QAs) between a biosimilar and the RP is the basis for establishing biosimilarity. QAs are measurable product characteristics that

describe the physical, chemical, biological, and microbiological properties of a drug molecule. Unlike generics, biologicals are molecules with intrinsic variability, which makes their QAs heterogeneous and susceptible to changes throughout the manufacturing process. Any differences that exist must be extensively analyzed to determine that they are not clinically relevant to the point of compromising the product's function, immunogenicity, and efficacy (22). Therefore, unlike a generic, a biosimilar must present clinical and non-clinical data that prove its similarity, that is, comparability studies must be carried out (this topic will be discussed in depth in section 3) (14,19,21,23).

3.2. Intended Copies, Biobetters and Standalone Biologics

Biosimilars should not be confused with intended copies, biobetters, and standalone products that are related but entirely different concepts (24). Physicians should not feel obliged to prescribe biosimilars based only on cost reasons, to make an informed decision before prescribing them for therapy or substitution for an RP, they need to know the differences between them (25).

Intended copies are copies of an RP, that do not follow a pathway consistent with EMA/FDA guidelines and WHO advise. As so, they are not available in highly regulated markets such as the US, Europe, and Australia but are marketed in less regulated countries. Because they are cheaper, accessibility to biologicals in these countries has increased. For example, reditux is an intended copy of rituximab that is available in India. This medicine has undergone a phase III study to confirm its efficacy but has not undergone a direct comparison with the original rituximab. Kikuzubam is another intended copy of rituximab that was available in some South American countries, however, it was withdrawn because of side effects and toxicity. There is no evidence that intended copies have the same efficacy, quality, and safety profile as RP. Even if the amino acid sequence is indeed the same, the pharmacological profile of the molecule can be affected, either by the presence of impurities, the formation of aggregates, or the occurrence of PTMs (post-translational modifications), for example. These medicines do not have comparative clinical trials to evaluate efficacy and safety or clinical trials with an adequate number of patients to determine equivalence / non-inferiority. They are also not announced in global biosimilar news websites and do not have a registered protocol in clinicaltrials.gov (or it is not followed or not verified) (3,17,25).

Biobetters, in turn, are deliberately modified versions of other biological drugs, to improve certain attributes of their pharmacological profile, such as dosage regimen, safety, efficacy, or immunogenicity (26,27). Their manufacturing process is similar to that of biologicals, however, it involves using various advanced methods such as albumin replacement,

pegylation (the addition of PEG), among others (26,27). Due to significant differences in molecular structure and molecule function, biobetters are considered new biological entities and must follow the standard approval pathway established by regulatory agencies rather than the biosimilar approval pathway (20). For example, insulin glargine is a biobetter which resulted from a change in the amino acid sequence of insulin, it was designed to delay the release of insulin monomers after subcutaneous administration (17). Darbepoetin alpha, is an altered version of epoetin, with an altered pattern of glycosylation, which prolongs the elimination half-life (17). Another example is neulasta, a biobetter of neupogen, whose dosage frequency is once per cycle of chemotherapy, while neupogen is once a day during the chemotherapy cycle. In addition, neulasta is more effective than neupogen, resulting in greater adherence. Lower dosage frequency, along with superior efficacy, means a lower economic load for each scheduled dose administration (17,25).

Finally, standalone biologics are developed and approved not as copies of an RP, but as new medicines, and their efficacy and safety are tested by comparison with a placebo or another valid comparator. So, a standalone is a biological me-too. This term can be applied to any biological medicine, but particularly when the drug in question is similar to one already approved and used therapeutically, but without validation of similarity by an extensive comparability study. It is important to bear in mind that this decision is purely strategic, as this medicine can perfectly be considered a biosimilar (17).

4. Development and Regulatory Approval of Biosimilars

4.1. Development of a Biosimilar

The development and approval pathway for a biosimilar differs substantially from that for innovative medicines (chemical or biological), as shown in Figure 1 (28).

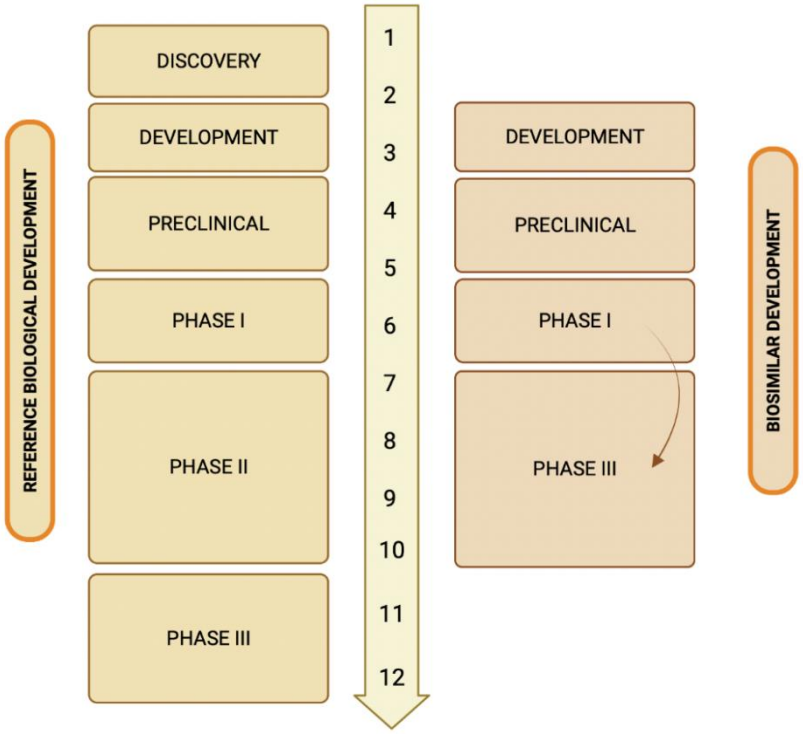

Figure 1 – Schematic illustration of the development phases and the timeline (in years) of reference biologic's versus biosimilar's.

The typical approval process for innovative biological medicines is approximately twelve years, which includes a relatively long research and development phase to produce an appropriate candidate molecule, which is then extensively characterized in the preclinical phase (20). Clinical development follows the progression of established phases I-II-III, followed by phase IV after commercialization. In the case of generics, their development starts with the drug molecule (already established and characterized) and only requires the production of the finished product and bioequivalence tests (17). As biosimilars are copies of marketed molecules with known product attributes, there is no need to carry out the initial discovery or efficacy phase (phase II), thus shortening the development time to eight or fewer years and reducing the development costs by 10-20% (5,20,29).

In other words, biosimilar medicines development lies somewhere between innovative drugs and generics. Like generics, the molecule is established from the start; but, unlike generics, the molecule is not easily reproduced or characterized (10,17). Thus, biosimilar manufacturers face a huge challenge: the manufacturing process of the RP is proprietary, i.e.,

its details are not publicly available – biosimilars are therefore expected to be produced, formulated, and administered under the same regime as the RP, without access to the know-how of the RP manufacturer. In this way, the biosimilar manufacturer must extensively analyze the RP and use a method of "reverse engineering" to be able to produce a product highly similar to the RP (12,17,30–32). Healthcare professionals must be conscious of the differences between the concepts of therapeutic equivalence (i.e., substitutability) and "comparability". Therapeutic equivalence is a term used when we are referring to generics, which means that generic and RP have an identical chemical composition and are bioequivalent (have the same pharmacokinetic profile). The term "comparability" is used in the context of biosimilars and means that the biosimilar and the RP have comparable efficacy and safety (but that does not mean they are identical, and it does not guarantee therapeutic equivalence) (33).

When a manufacturer develops a new biosimilar, a well-established, step-by-step approach based on sound science and quality risk management needs to be adopted (28). Then, "quality-by-design" (QbD) strategies are used, which allow the biosimilar to achieve a high degree of similarity to the RP. It is essential to select an appropriate RP, obtain the reference active principle, identify the RP's "quality target product profile" (QTPP) and Critical Quality Attributes (CQAs) and develop a manufacturing process that allows matching the RP attributes. So, although the concept of biosimilar applies to any biological, the success of this approach depends on the ability to characterize and match QTPP (14,18,28).

First, the RP quality attributes (QAs) (structural, functional, and other analytical properties) must be defined. The range of variation for any quality attribute that has a direct impact on the effectiveness or safety of the RP (CQAs) must be carefully measured, using multiple batches of drugs: these are used to profile the quality of the target product of the proposed biosimilar (3,23,28). In other words, CQAs are chemical, physical, biological, and microbiological characteristics that are defined, measured, and monitored continuously, to guide the clinical profile and establish clinical comparability (14,21,28). For example, the CQAs of Infliximab (which is the RP of the biosimilar CT-P13) are numerous and include those related to the structure (primary and higher-order structures, glycosylation profiles), biological function (cytotoxicity, receptor binding affinity), content (protein concentration) and impurities (host cell protein or DNA) (23).

Next, the expression system (cell line and expression construct) is selected, and this is a fundamental decision because this step can affect the translational and post-translational modifications of the biosimilar and determine the number and nature of impurities and product contaminants (31). Although biosimilars are expected to have the same amino acid sequence

as the RP, low-level sequence variants can be detected by highly sensitive methods. These variants can be derived from mutations in DNA or incorrect incorporation, resulting from a mistranslation or improper acylation of the tRNA. In addition, biological products are subject to PTMs during cellular expression, including N- or C-terminal modifications such as amino acid cleavage, N-acetylation, methylation, and most importantly, glycosylation (this affects biological function). Purity profiles and the final product are also influenced by purification methods, formulation and storage conditions, and container closure systems. Manufacturers of RPs use proprietary growth and purification conditions and cell lines specially adapted for their processes, so knowledge of the protein sequence or the cells used is not enough for the biosimilar manufacturer to produce the same biological product. Differences in structure between the biosimilar and the RP need to be minimized because even small differences can potentially affect PK, efficacy, safety, and immunogenicity (28).

4.2. How to Build the Evidence for Biosimilarity?

The biosimilar investigation pathway is not intended to demonstrate superiority or inferiority between the proposed biosimilar and the RP, but rather to demonstrate that the biosimilar does not have a decreased or increased safety and efficacy profile compared to the RP (10). The demonstration of biosimilarity is achieved through a step-by-step approach, as recommended by the EMA and the FDA: first, a study of physicochemical and biological comparability (quality studies) is carried out, then non-clinical comparability (*in vitro* and *in vivo* studies) and, finally, clinical comparability (4,12,14,15,34,35). The clinical comparability study is generally carried out in successive steps, starting with PK and, if possible, PD studies, followed by at least one clinical trial of efficacy and tolerance (4). However, in most cases, quality studies performed *in vitro* are sufficient to establish that the changes are not clinically relevant. It is important to note that the two products do not need to be identical, what is needed is that there is no clinically significant change (i.e., the proposed biosimilar and the RP need to be comparable) (17).

Therefore, all steps have a serious contribution to the (bio)physical characteristics, and to establish biosimilarity, no step can refute or overcome significant differences in the previous steps and all three must be satisfactory. So, the development of a biosimilar can be as extensive as that of the RP, but with a different emphasis: in the manufacture of the biosimilar, the emphasis is on comparability in the early stages of development, while for a new biological agent the emphasis is establishing clinical efficacy and tolerability (14) – as shown in Figure 2.

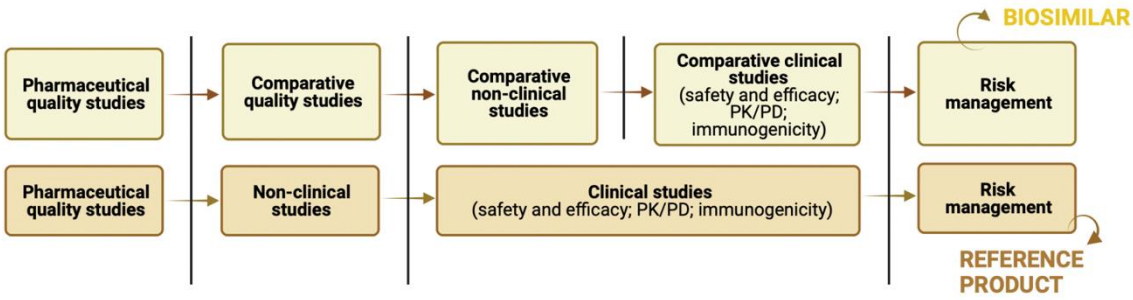

Figure 2 – Building evidence for biosimilarity – comparison of data requirements for approval of a biosimilar versus an RP.

4.2.1. Demonstration of Analytical Similarity – Comparative Quality Studies

Analytical analyzes constitute a repetitive and iterative process, whose objective is to compare the quality of the proposed biosimilar with that of the RP. These assays account for most of the effort involved in biosimilar development, allowing a highly sensitive determination of the degree of similarity (28,36). Quality comparability assesses molecular structure as well as functionality and should be demonstrated with comprehensive analytical characterization, relevant studies of receptor binding, and bioassays. These studies are carried out through *in vitro* assays, which are sensitive techniques capable of detecting small clinically relevant differences between the biosimilar and the RP (14,18). If slight differences in structure (such as glycosylation variants) occur, the product can still be considered a biosimilar, since the structural differences do not have a clinically significant impact on efficacy and/or safety (14). It is necessary to test multiple batches of RP over a predetermined period to build a complete QTPP and ensure that the produced biosimilar closely reflects the RP (14,28).

Quality attributes (QAs) are compared using analytical methods such as Surface Plasmon Resonance (SPR), Enzyme-Linked Immunosorbent Assay (ELISA), Mass Spectrometry, and Flow-Cytometry. The QAs to be evaluated include physicochemical properties, biological activity, immunochemical properties, purity and impurities, quantity, strength, thermal stability profiles, and other modifications such as oxidation and deamination (14,18,28).

The PK comparison includes the evaluation of PK parameters and also the determination of the composition, physical properties, primary structures (amino acid sequence and disulfide bond), and higher-order structures (e.g., local, and three-dimensional conformation) of the biosimilar. As mentioned above, the target amino acid sequence, which is expected to be the same as the RP, must be confirmed, and the N- and C-terminal amino acid sequences, free SH groups, and disulfide bonds must be compared. If there are PTMs,

such as glycosylation, oxidation, deamination, these must also be characterized. If there are carbohydrate structures, such as general glycan profile and glycosylation patterns, they need to be compared (14,18,21,28). The determination of biological activity is dependent on the nature of the product and generally comprises mAb-antigen binding, Fcγ receptor binding, and FcRn binding (14). The characterization of the purity and impurities related to the product and its manufacturing process helps to guarantee its safety, and they must be determined and compared qualitatively and quantitatively, through a combination of analytical procedures (28). The shelf life of the biological source and any effect on its quality profile must be considered. All process-related impurities must be determined (e.g., host cell DNA and proteins, reagents, downstream impurities, etc.), as well as their potential risks (e.g., immunogenicity) (18). Thermal stability assessment examines forced degradation profiles and degradation products (28).

In the case of biosimilars mAbs (which some of their QAs are represented in Annex B), the assessments of the biological activity to bind to the Ag, the connection to the Fcg receiver, the FcRn binding, the antibody-dependent cellular cytotoxicity (ADCC), and the complement-dependent cytotoxicity (CDC) must also be carried out. In addition, the affinity and Ag binding specificity of the biosimilar and the RP must be compared. So, depending on the mAb's mechanism of action, the impact of the difference in biological activities related to the Fc regions on efficacy and safety will be different: if the mAb exerts ADCC activity, the difference in FcgRIIIa binding and ADCC activity must be carefully considered; if, on the contrary, ADCC activity is not included in the mAbs mode of action (e.g., mAb against soluble monomer Ag), it is possible that the difference in binding does not have a significant impact on the mAbs efficacy and safety (18).

4.2.2. Establishing Non-Clinical Biosimilarity

The non-clinical comparability exercise aims to assess the similarity between the biosimilar and the RP in terms of its mechanism of action, its functional activity, and its quality attributes (37). In this way, PD studies are carried out *in vitro* (physicochemical and laboratory analyses), to analyze the binding and activation (or inhibition) of physiological targets and the physiological effects on cells. In this way, the pre-clinical comparison of PK and PD can be quite useful to reduce the residual uncertainty regarding similarity (28). *In vivo* PD studies are only used if there are no *in vitro* models that meet the required parameters (15,34).

The use of animals in research (*in vivo* studies) continues to be a controversial and sensitive issue, and guidelines recommend that their use should be minimized or eliminated

wherever possible, by implementing, for example, the principles of the 3Rs (Replacement, Reduction and Refinement). However, non-clinical evaluation using *in vivo* studies may be needed to complement the information obtained during the analytical phase of biosimilar development. In particular, the need for these studies may be motivated by the presence of potentially relevant QAs that were not detected in the RP, the presence of potentially relevant quantitative differences in the QAs between the biosimilar and the RP, and any relevant differences in the formulation, for example, use of excipients not widely used for proteins derived from biotechnology (14).

If an *in vivo* assessment is deemed necessary, then the focus of the study will depend on the need for additional information. The assessment may include a quantitative comparison of the PK and PD profiles of the biosimilar and RP, including dose concentration-response. In the case of safety studies, and if non-human primates are the only relevant species, a flexible approach should be considered. Conducting non-relevant species toxicity studies (i.e., to assess only non-specific, impurity-based toxicity) and standard repeat-dose toxicity studies in non-human primates is not recommended – however, in certain cases, it may be necessary, such as when a biosimilar is produced in a new type of cell or organism, or when the formulation includes new excipients. Quantitative and qualitative alterations in product-related variants (e.g., glycosylation), which may cause hypersensitivity, should be clinically evaluated. (14,18,28). Though immunogenicity studies in animals are not predictive of immunogenicity in humans, blood samples can be collected in animal studies for additional assessment of PK/toxicokinetic data, if necessary. Safety pharmacology, reproductive toxicology, and carcinogenicity studies are not required. Also, local tolerance studies are not normally required; however, if excipients are introduced for which there is little information regarding the route of administration, they may need to be evaluated (14,28).

4.2.3. Clinical Considerations – The confirmatory role of phase I and phase III clinical studies

Clinical studies constitute the third stage of the comparability study (36). As mentioned, the establishment of biosimilarity focuses, above all, on pre-clinical aspects and, particularly, on the quality of the biosimilar. Thus, the number and scope of clinical studies executed depend on the degree of residual uncertainty with respect to biosimilarity following the earlier analytical assessment (and non-clinical *in vivo* testing, if executed) – Figure 4 (14,28).

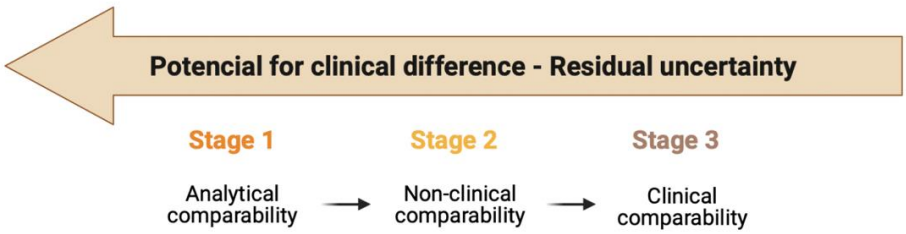

Figure 3 - Residual uncertainty along the stages of the comparability study of biosimilars.

Briefly, in this third step of the comparability study, the aim is, through the analysis of analytical data or previous studies, to rule out clinically relevant PK/PD, clinical safety (immunogenicity), efficacy, extrapolation, and PV differences – and thus confirm the biosimilarity between the proposed biosimilar and the RP (18,19,28). That is, while reference biological medicines are evaluated in controlled trials to demonstrate their clinical benefit, the purpose of biosimilar clinical trials is only to demonstrate clinical equivalence between the potential biosimilar and RP (18,19).

4.2.3.1. Pharmacokinetic and pharmacodynamic studies

Clinical development of a biosimilar begins with a study designed to demonstrate the PK and PD similarity of the proposed biosimilar and the RP (28). The study design depends on several factors, namely the clinical context, safety, and PK of the RP, and must be defined and justified before it is carried out (14,18).

PK assessments are needed to compare the biodisponibility of the drug, which includes absorption, disposition, time dependence, and binding to blood components. PD studies, in turn, ensure that the biosimilar's efficacy in the target tissue is equivalent to the RP, and that the mechanism of action is identical. In some cases, comparative PK/PD studies may be sufficient to demonstrate clinical comparability (14).

These studies must be carried out in an appropriate population, and whenever possible, it is preferable to use only healthy individuals, as this guarantees a homogeneous population, composed of immunocompetent subjects who are not receiving any concomitant medication (28). Generally, single-dose studies are sufficient to characterize absorption and compare different routes of administration. It should be noted that soluble receptors can bind to the therapeutic protein, resulting in an altered PK profile by changing clearance or volume. Likewise, the binding capacity to plasma proteins (albumin, acid α-glycoprotein) should be studied when relevant. When performing these PK assessments, several factors need to be

considered, including chemical modification of proteins, variability between individuals (e.g., age and weight), immunogenicity, drug interactions and special populations (e.g., renal, or hepatic impairment) (14).

4.2.3.2. Efficacy studies

Present regulatory guidelines do not demand comparative clinical efficacy studies in all circumstances. FDA declares that a comparative clinical study is necessary "if there is residual uncertainty about whether there are clinically meaningful differences" (38) between the proposed biosimilar and the RP "based on structural and functional characterization, animal testing, human PK and PD data, and clinical immunogenicity assessment" (38). The complexity of the RP, the degree to which the mechanism of action of the active substance is understood, and the availability of a PD endpoint that correlates with efficacy are factors that assume the type and extent of clinical data necessary (38–40). EMA, on the other hand, states that although comparative PK/PD studies remain essential, the rigorous requirement for comparative efficacy studies for some product categories along with comparative safety/immunogenicity studies has been (or is planned to be) waived in certain circumstances (15,34,41).

Efficacy studies make it possible to analyze the significant differences that exist in terms of treatment efficacy, that is, their objective is not to establish efficacy *per se*, but to demonstrate the comparability of clinical performance (14). These studies require randomized parallel-group comparative clinical trials (preferably double-blind trials), as well as appropriate efficacy endpoints – they must be sufficiently sensitive to detect potential product-related differences while minimizing the influence of patient or disease-related factors. A sensitive study population should be representative of the one included in the approved indication for RP and should be sufficiently sensitive to detect small differences between the efficacy of the proposed biosimilar and the RP. Factors such as prior lines of therapy, the effect of concomitant medications, and the gravity of the disease are also relevant to sensitivity (18,42).

4.2.3.3. Safety evaluation

Knowing the safety profile of the biosimilar is a crucial aspect of the comparability study. As with any new biological medicine, the biosimilar's safety profile is built across the entire clinical program – during phase I PK/PD studies and phase III direct comparison studies (14).

The type, severity, and frequency of adverse events (AEs) are evaluated and critically compared between the biosimilar and the RP to ensure biosimilarity. Any safety concerns that may result from differences in the manufacturing process must be considered (14). Moreover,

immunogenicity must also be intensively studied, because of the potential immunogenic nature of biologicals. The duration of the immunogenicity study should be justified on a case-by-case basis because it is dependent on the duration of the treatment, the release of the product into the blood circulation, and the time it takes for the immune response to appear. If there is an increase in the immunogenic profile of the biosimilar in relation to the RP, it can become a problem for the risk-benefit analysis (the same does not happen if the immunogenic profile is lower in the biosimilar) (4,14).

4.3. Regulatory Concerns

In the last fifteen years, about one hundred biosimilars have been approved by EMA and/or the FDA, and this number is predicted to grow even more in the next years. For their approval it's necessary a robust regulation (20,21). The primary responsibility of regulatory authorities and manufacturers is to avoid any clinically significant structural differences that could adversely affect the efficacy and safety of the proposed biosimilar. This is achieved by evaluating and demonstrating a high range of structural and functional similarities between the biosimilar and the RP (10).

Biosimilars have very particular and exclusive approval conditions and implementing an abbreviated licensing pathway can present several challenges (28). Therefore, the EMA and the FDA had to develop specific and consistent regulatory guidelines, for the approval of biosimilars – the EMA's guidelines are presented in Annex C (19,34). However, divergencies exist between the regulatory agencies, so the number of biosimilars approved in the various markets is very different (12). EMA was the first regulatory agency to approve, in 2004, the legal framework for biosimilars (15). It was followed by the FDA, which has adopted the same principles. Both agencies recognized the complexity of developing biosimilars, highlighting the fact that all biosimilar candidates have unique and specific aspects and therefore will require case-by-case targeted development programs. WHO has made recommendations to support the worldwide development of these products, requiring at least the existence of clinically relevant parameters, including PK, PD, safety, efficacy, and immunogenicity data, to consider biosimilarity (14,28,40). If there is enough evidence of biosimilarity from all other previous non-clinical data, efficacy studies can be waived. More extensive toxicological and/or clinical studies are needed when differences are identified to address residual uncertainties and undesirable immunogenicity (12,27).

US and EU laws state that a RP must be approved by local jurisdiction. Therefore, for approval in the US, the proposed biosimilar must demonstrate its similarity to the RP approved in the US, and for EU approval, it must be similar to the RP approved in the European

Economic Area (EEA) (6,28). Recognizing the complexity and expense associated with the development of biosimilars, both agencies have implemented measures to allow, when scientifically justified, the use of comparators of foreign origin in comparative clinical studies. From a regulatory and legislative perspective, the acceptability of reliance on clinical data generated using a comparator of foreign origin depends on the successful establishment of the "scientific bridge". The "scientific bridge" between the product of local origin and that of foreign origin must consist of a comprehensive assessment of the analytical similarity of the proposed biosimilar with both comparators. In addition, this bridge must be complemented with a three-arm PK similarity study, in which bioequivalence is recognized between the candidate biosimilar and each respective comparator, as well as between the two comparator arms (27,28).

Another regulatory consideration, exclusive of the US, is the determination of interchangeability. Under the US law, an interchangeable biosimilar is a product that is biosimilar to the RP and is expected to produce the same clinical effect in any individual (39). When the RP is substituted with a biosimilar, the risk in terms of efficacy and safety cannot be greater than if there is no substitution. EU regulatory framework on biosimilars does not include specific requirements for interchangeability (15). Although biosimilars are centrally approved by the EMA, Member States (MSs) make substitution policies individually (27,28).

Another requirement for the successful adoption of biosimilars includes naming criteria and safety monitoring or PV. The use of distinguishable names has been discussed: adding a four-letter suffix to the international nonproprietary name (INN) to prevent inadvertent substitution by a pharmacist based on a lack of product name specificity. In addition, distinguishable names are important from a PV perspective to ensure proper attribution of adverse events to the correct manufacturer (27,28).

These issues of interchangeability, substitution, extrapolation, and nomenclature will be explored in Section 5.

5. Post-Marketing Monitoring of Safety of Biosimilars – Pharmacovigilance

PV, in accordance with Good Pharmaceutical Practices, aims to identify, quantify, evaluate, and avoid the risks associated with the use of commercialized products, with the aim of improving the safety of medicines, in defense of users and public health (8,43). Data from clinical studies, namely on biosimilars, are usually insufficient to identify rare AEs and, in addition, their clinical development program is poorly suited to identifying tolerability risks, as it is known to be shorter than the RP's. Therefore, it is recommended to continue monitoring the clinical tolerability of biosimilars during the post-marketing phase (4,10,28,33) – it is

especially significant for these medicines since their safety varies due to immunogenicity, hypersensitivity reactions, and an increased risk for other AEs, and because of their vulnerability to variations in the manufacturing process (8,33,44). The manufacturer needs to have a PV system in place that can detect, evaluate, and prevent the appearance of a drug-related AE during its manufacturing. So, PV systems should not simply track types and severities of AEs to identify new class-based risks but should also be robust enough to detect the number of times that AEs occur over time (8,9,43). Within the authorization process, the applicant must submit a description of the PV program and a risk management plan that complies with current EU legislation and PV guidelines. Any specific tolerability monitoring imposed on the RP must be adequately addressed in the biosimilar's pharmaceutical co-surveillance plan, and immunogenicity must also be considered in this context (4).

After the product is introduced into the market, EMA have well-established PV programs for the monitoring of AEs. EudraVigilance is the EMA network for reporting and evaluating suspected AEs during development and following marketing authorization. Information on drug safety is collected through spontaneous reports by healthcare professionals and patients (9). Preferably, these reports should include as much information as possible, including the nature of AE and information on the drug (e.g., proprietary name, INN, lot number, and dosage given). However, correct causality can be difficult to assess, since patients who are undergoing therapy with biopharmaceuticals are often in polytherapy and are individuals with serious diseases and/or risk of life. Moreover, AEs are frequently not reported, or the reports are incomplete. In addition, the rules for reporting vary from country to country (9,33).

In all medicines, the Summary of Product Characteristics (SmPC) and the Information Leaflet (IF) must include a text urging to report any suspected AE, through national spontaneous reporting systems and/or official forms available on the internet (43). In the meantime, a new concept has been introduced by the latest EU PV legislation, where a list of drugs subject to additional monitoring during a certain period has been released. For that, these drugs are identified with a black symbol (inverted triangle) with corresponding text in the SmPC and IF. With this new approach, there was a strengthening of the PV of all medicines, increasing transparency, communication, and trust (45,46).

After more than fifteen years since marketing the first biosimilar in Europe, no significant differences have been reported in terms of the safety profile of biosimilars. However, their monitoring remains extremely important, particularly in pediatrics, as the risks and comorbidity profiles in children may be different from those in adults (9).

6. Controversies in the Use of Biosimilars

Despite the numerous benefits that biosimilars bring, there are significant differences, namely, in their use, the cost reduction achieved, and their market share, which raises questions regarding efficacy, safety, immunogenicity, extrapolation, exchange, and interchangeability of these drugs (46,47)

6.1. Immunogenicity

Immunogenicity is the ability of a specific substance to cause an unwanted immune response that is induced by more than one factor (48). This immune response is complex and, in addition to the formation of Abs, it also involves other events, such as the activation of T cells or the activation of the innate immune response (30,48). The immunogenicity profile is a key element for obtaining regulatory approval for biosimilars, that is, it is an essential component to establish biosimilarity between the proposed biosimilar and the RP, being evaluated through rigorous quality, non-clinical and clinical studies (3,4,30,42,45,48–50).

As previously mentioned, biological proteins have a high molecular weight and a very complex composition. For this reason, when these drugs are administered to patients, they can produce undesired immune responses, stimulating the formation of anti-drug antibodies (ADAs), which may cause immune-mediated toxicity (retarded hypersensitivity and anaphylactic reactions) or compromise the effectiveness of treatment (45,50). However, immunogenicity alone does not translate into safety, since this adverse reaction is very rare and, in most cases, the immunological reaction is not even related to clinical consequences (e.g., ADAs can be transient) (3,15,34,45,51). Moreover, the nature of the reactions is related to several factors, such as the characteristics of the product (alterations in the production process, the stability characteristics, and the protein structure during storage); the treatment-related factors (risk is related to how it is administered – subcutaneously or intravenously); and the patient/disease factors (e.g., age, immune system status, genetic history, concomitant medication) (4,26,45,47). It is also important to mention that it is very unlikely that harmful immune reactions will occur once changes have occurred in the manufacturing process or after switching from one biological to another, as the comparability studies show that the batch obtained has the same quality and is free of impurities or aggregates that could cause immunogenicity (15,30,35). Finally, another very important aspect is that immunogenicity is always subject to post-authorization monitoring, which must be guaranteed by manufacturers, pharmacists, and physicians (52). This step is extremely important for detecting rare but potentially dangerous immunological reactions that can only be identified after an extended

follow-up period of several patients – therefore, immunogenicity assessment must be part of Risk Management Plans (RMP) post-authorization and PV activities (15,30,35,48,52).

The EMA has published useful guidelines on immunogenicity, however, as each product has such specific considerations, it is difficult to define an analogous approach for different biologicals, so each manufacturer must justify the method used to evaluate it (1,34).

6.2. Extrapolation

One of the central concepts in the development and approval of biosimilars is the concept of extrapolation – it allows the biosimilar to assimilate the clinical indications of the RP, without the need to carry out clinical trials for these same indications (16,46,49,51,53). However, to be considered supportive of extrapolation, data should be based on studies using a sensitive clinical model to detect potential differences in efficacy, safety, or immunogenicity between the RP and the potential biosimilar. The population used for this sensitive study may include a different patient population than that used in pivotal clinical trials of the RP. The primary endpoints measured may be the same (or not): PD measures are considered sensitive clinical endpoints and may be selected as primary endpoints of the biosimilar clinical study (6,12,28,36). Moreover, to be considered supportive for extrapolation, it is also necessary that the indications have the same molecular mechanism of action, include the same receptors, have a similar dose-response link and a similar pattern of molecular signaling upon target binding, and have similar location and expression of the target (6). The entirety of the data should also enclose well-described PK and biodistribution evidence as well as enough description of safety and immunogenicity to confirm that the biosimilar does not have exclusive or extra safety issues when compared with the RP (6,23,35).

This issue has been the subject of immense criticism and has been discouraged by several professional medical societies (40,45). As the clinical part of the comparability study between a biosimilar and its RP is typically limited to one or two comparative phase III clinical trials, some clinicians are wary of using the biosimilar for indications in which it has not been studied but for which the RP has been approved. However, since the extrapolation is based not only on clinical data, but also on structural, physicochemical, functional, and non-clinical data, this point of view must be clarified (1,6,40,45,48).

Thus, the decision to allow extrapolation of data for indications is the responsibility of each regulatory agency. The EMA and FDA guidelines allow extrapolation of indications when there is enough scientific justification and when all evidence demonstrates biosimilarity and a well-known mechanism of action (39,40). For example, in the case of Infliximab, which is indicated for various diseases (ulcerative colitis, Crohn's disease, plaque psoriasis, psoriatic

arthritis, rheumatoid arthritis, among others), some regulatory agencies, such as EMA, have approved it for all RP's indications, while others do not (14,45). In accordance with EMA approved regulation for reference biological drugs, all data that comes from clinical development are contained in the SmPC (40). Therefore, the extrapolation of therapeutic indications between reference biologicals and biosimilars is accepted, if it is scientifically justified and considered through the analysis of all analytical, non-clinical, and clinical data (14). However, expansion or restriction of indications should not be accepted, and non-approved indications are considered *off-label* (5,30,45,48).

6.3. Interchangeability and Substitution

Once a biosimilar is authorized by a regulatory agency, it can be prescribed with guarantees of efficacy and safety, for all indications authorized in the SmPC (47,54). For this reason, a physician, when starting treatment on a patient, can introduce an RP or a biosimilar (48,54). But the questions are: can physicians replace the RP (which is being administered) with a biosimilar? can the RP and biosimilar be used interchangeably with one another? To understand these questions, it is important to understand the terms "substitution" and "interchangeability" which, although being very similar, are quite different concepts, and should not, therefore, be confused (5,20,45,46,53).

Substitution is the act by which the pharmacist replaces a drug with a similar one, without the need for the physician's consent or the patient's approval since there is confirmation that the repeated exchange between these two drugs does not constitute an additional risk to the safety and does not reduce the effectiveness of therapy (5,45,46). Interchangeability is the medical act by which a drug is replaced by another similar one, but the physician's consent and the patient's knowledge and approval are required (5,14,45,46,53,55).

In all these cases, it is important to highlight the physician's role as the last link in the decision chain for choosing the most appropriate drug for the patient. However, for the physician to choose and prescribe the most appropriate treatment, regulatory bodies must position themselves regarding interchangeability and establish guidelines that detail when and how the exchange can be carried out. Nonetheless, at this point, there is great uncertainty, since the opinions of regulatory agencies around the world are heterogeneous, and the interchangeability and substitution of biosimilars are not characterize in detail – this is because biosimilars are not interchangeable *per se* (5,45,55). Predominantly, regulatory agencies and scientific corporations consider that biosimilars can be prescribed to "naive patients" or to chronically ill patients who have already been successfully treated with biologicals – "naive

patients" are patients who have never been treated with biologicals ("primary naive patients") or who were treated and then experienced a wash-out period (5,9,45,55).

FDA was the first regulatory agency to legally define interchangeability (in January 2017) (39,40). For an interchangeable status to be granted, the FDA requests that studies be performed that demonstrate biosimilarity as well as pre-marketing studies that address the multiple and reverse exchange of biosimilars and RPs (38–40). Furthermore, clinical trials of PK and PD must be validated at the beginning of the development. Therefore, according to FDA legislation, a biosimilar is considered interchangeable with RP when the data presented show that there are no increased risks in terms of safety or decreased efficacy (35,38,39,53). When a biosimilar is considered interchangeable with RP, FDA allows automatic substitution, without the intervention of the prescribing physician (6,9,19,31,40,53)

Contrary to what occurs in the US, in EU each country is free to decide whether the substitution is allowed or not, because EMA does not have the authority to consider a biosimilar as interchangeable in all EU countries (40). In the case of Portugal, we do not have regulations in this regard, unlike countries such as Germany and Italy, which have clinical guidelines that prohibit automatic substitution, and Spain, Norway, and Ireland, which have laws that specifically prohibit substitution (2,36,40,56). France was the first European country to allow the substitution of biosimilars, but it is only allowed if a new treatment is started (naive patients), if the biosimilar belongs to the same pharmacological group as the prescribed drug, and if the physician does not expressly forbid it (12,36). In Finland, the Finnish Medicines Agency (FIMEA) established that biosimilars are interchangeable with their RPs, provided they are under the supervision of a healthcare professional (but they do not describe their position on substitution) (2,30,56,57). In the Netherlands, substitution by other biosimilars is allowed, but never by the RP. In summary, although these countries have accepted the relevance of biosimilars, the legislation on their interchangeability is still far from being visible (6,9,15,19,30,40,57).

6.3.1. Automatic Substitution

Automatic substitution is another term used and refers to when the pharmacist is required to dispense generic drugs in place of prescribed innovator products without the knowledge or consent of the treating physician (5,45,46,53,55).

Automatic substitution is applicable for most generics and produces cost savings. However, there are circumstances where it is not advisable and may compromise safety and PV programs. This happens, for example, with modified-release theophylline and calcium channel blockers – in these drugs the difference between the therapeutic and the toxic effect

is minimum, so it is not possible to assume that the biosimilar will have the same risk/benefit as the RP (28,43). In some US states and European countries, automatic substitution is prevented by placing the drugs on "do not substitute" lists, and other European countries trust the training and expertise of physicians and pharmacists to prevent inappropriate substitution (1,34,41). When the distribution systems allow or encourage automatic substitution, and if physicians and/or pharmacists do not recognize the potential risks involved, inappropriate substitution can occur. In this regard, in February 2007, French legislators established a risk prevention measure, that differentiates biosimilars from generics and prohibits automatic substitution with biosimilars (1,34,41). Automatic substitution is not appropriate for biopharmaceutical products. As mentioned before, biosimilars are not generic versions of innovator products and small differences between biosimilars and RPs may affect clinical outcomes (5,10,17,20,23). Besides, if automatic substitution is permitted, patients receive various biopharmaceutical products over the course of therapy, which makes it difficult to collect PV data: if an AE were to occur after switching from one to another without documentation of the product change, the event wouldn't be able to be related to a specific product during the PV assessment, or it could be attributed to the wrong product. It is fundamental that physicians be aware of the exact biopharmaceutical product their patients are receiving (5,17,43).

6.4. Nomenclature

In the post-marketing period, it is essential to ensure a precise prescription and to avoid confusion between the biosimilar and its RP (as well as between the biosimilar and other biosimilars), so a specific nomenclature is necessary (4,10). This nomenclature will be extremely important to monitor the use of the drug throughout its life cycle, allowing to report and track adverse events (45,49,51,58)

Organic products are so complex that it is impossible to use short, usable, and descriptive names, that is, their definition is very difficult and subjective – this is because the same criteria are not used to define unique products (4,51,58). Active substances can be named based on their structures, approvals, and/or how they are marketed, however, this is not the case with biopharmaceuticals, as their naming involves identifying changes to the existing product, that is, we are considering it as a new and unique product, which requires a new name (4). But there are several different opinions: some consider that, as it is a product with a new formulation, a significantly altered processing, a new approval, a new trade name, and a different manufacturer, among other reasons, it is considered a "new" product and, therefore, it requires a new name; others, on the contrary, consider these products to be

similar enough to keep the same name. So, with all these adversities, biosimilarity and approval of molecules is relatively easy when compared to the task of determining what is unique and different, how relevant the differences are, and how to define, name, and describe biosimilars (4,58).

WHO collaborates closely with INN experts to select a single globally acceptable name for each active substance to be marketed as a pharmaceutical. However, to achieve the intended objective in the post-marketing of biologicals and biosimilars, INNs cannot be used as the only means of biological identification. INNs work well for generic drugs, but not for biopharmaceuticals, as in this case even the most similar products must be considered different and unique (42,58). Using the INN, it is hard to attribute AEs to a specific product, then it is more appropriate to use the brand name, or the INN plus the brand name or some other unique identifier. Therefore, it was suggested that a Greek letter or a combination of several letters be appended to the end of biopharmaceuticals' INNs to make biopharmaceutical names "more unique" (17,45,59). However, even these names are not unique, and the same name is still often used for different products (with different manufacturers, bioprocessing, formulations, delivery systems, etc.). For example, "interferon beta-1α" applies to several marketed products. That is, as the number and diversity of biosimilars increase, INNs become increasingly irrelevant (17,58). Another alternative then emerged, proposed by WHO, which consists of using a biological qualifier (a four-digit code) to distinguish biosimilars from reference products (17,40,45,59).

Some regulatory bodies suggest that the INN system should not be used to prescribe biosimilars. In 2012, the European Commission emitted Directive 2012/52/EU, establishing that the use of brand names is mandatory, to ensure the accurate identification of biologicals – this requirement also applies to biosimilars. In addition, as AEs can result from unintentional changes during manufacture, besides the brand name, it is also suggested that the regulatory agencies de informed of the batch number, to ensure proper traceability. However, most physicians only report the brand names, disregarding the batch number indication (17,40,51,59). Futermore, with the introduction of this new Directive, the replacement of biosimilars (as they are marketed as branded products, that is, never seen before) becomes more difficult, as it causes confusion and makes their acceptance difficult. Therefore, the type of names assigned to biosimilars will greatly affect their marketing, making the replacement of interchangeable biologicals (where permitted) less likely (40,44,58).

7. Implementation of a Biosimilar Model in a Hospital Context

7.1. Economic aspects of the use of biosimilars

Considering the substantial increase in public expenditure on medicines (hospital and outpatient clinics) over the last few years (an increase of 30%), it is essential to avoid waste. For this reason, biosimilars are a valuable opportunity in this context, since they promote competition, generating greater accessibility, with an impact on sustainability and access, without altering the quality of care, which makes them more cost-effective therapeutic options (60). Cumulative savings between 2016 and 2020 in the EU and the US are estimated to be between €49 billion and €98 billion. Savings derived from the entry of biosimilars into the market can alleviate costly health budgets and open budget space for new treatment options. Furthermore, biosimilar intake may increase the patient's access to biological therapies (61). The implementation of the use of biosimilars promotes a positive impact not only at an economic level but also at a social level, in terms of public health. In this context, the main differences between the use of biological vs biosimilar medicines are outlined in Annex D.

Europe has shown a strong adoption of biosimilar medicines, and in recent years these medicines have gained more than 7% of the organic market, this growth is related to the increase in the market of biosimilars in the areas of immunology and oncology (16,34,49). After more than 15 years of experience with biosimilars in Europe, with more than 2000 million patients/day of clinical experience, it can be said that biosimilars have a high standard of quality, safety, and efficacy, duly validated at the European level by the EMA (60).

In Portugal, between 2014 and 2021, there was a 51% increase in expenditure on medicines in hospitals, which corresponds to an increase of 488€ million, according to data from Infarmed IP (62,63). According to studies conducted in 2021, the use of biosimilars allowed greater access to biological therapies, with 3 049 424 patients being treated daily (60–62). Currently, biosimilars occupy about half of the market share of Portuguese biological medicines, with 18 biosimilars approved and 14 commercialized. However, only filgrastim, which appeared on the market in 2008, has a 100% share of biosimilar use. Somatropin, which entered the market in 2006, only has a usage share of 22.7% (60). The decision on the adoption of biosimilar medicinal products is closely related to economic studies and price but also depends on the recommendations of the CNFT (60). It is known that the pharmacological class with the greatest burden for the National Health Service (NHS) are immunomodulators, with an approximate value of 426€ million (by 2020) – which corresponds to 31% of the total expenditure on medicines. Therefore, a reduction in the cost to bear with these medicines allows for very significant savings for the NHS.

7.2. Positioning of the Portuguese Association of Hospital Pharmacists (APFH)

APFH has established its position on the use of biosimilar's therapeutics in Portuguese hospitals (64). The validation of the prescription of these medicines is the responsibility of the hospital pharmacist and must be the limiting step of the medicine circuit (64,65). The description of the medicine, dose, route of administration, frequency of administration, period of administration, pharmaceutical form, clinical indication, and clinical data must be recorded. This data is essential to prevent problems that may occur outside the internal circuit of the hospital (64). A medicine circuit must be created by the pharmaceutical services, and everyone involved in the process (physician, nurse, pharmacist, and technician) should be able to follow it – for this purpose, the brand name and batch number of the medicine must always be registered (64,66).

The preparation of the biosimilar in the hospital pharmacy, under aseptic conditions, must be carried out by technicians with adequate training and supervised by pharmacists (64). The label must follow the standards used in clinical trials, including patient identification, shelf-life, batch number, and time of preparation, ensuring that the medicine is always recognized at any time (64). The transport of the medicine in the hospital must be carried out by properly trained personnel in a controlled temperature environment (64). The delivery protocol must include a record of the batch number that will be administrated to the patient and proof that the medication arrived in the infirmary under required conditions, namely temperature, preferably with instrumental control of temperature and humidity. In the infirmary, the medicines should be conserved under the recommended temperature conditions and in accordance with the information provided by the pharmaceutical services (64). These services must ensure that all aspects of the biosimilar and the delivery of the patient card be evaluated, guaranteeing the continuity of the cold chain inside and outside the hospital (64).

The selection criteria for biosimilars should not be limited to the price and should contain, among others, proposals to avoid stock breakage, availability of several dosages (if any), shelf life that respects the turnover of the medicine and preferably single batches. Integrated management of biosimilar purchases should be carried out to ensure therapy for at least nine months (64,65).

Each hospital has its own rules and procedures for dispensing biologics and biosimilars (60,64,65). Risk management plans for biologics and biosimilars should be known. These plans are documents that are part of the marketing authorization for medicinal products and have been assessed and approved by the EMA (57,66). These plans should define specific risks of the different classes of biotechnological and biosimilar information that are identified. Suppliers

should be asked to change the manufacturing or packaging process so that this information is included in PV. The safety alert card that is delivered to the patients is one of these risk minimization activities that should be ensured by pharmacists. Data related to the treatment and specific to each medicine, must be recorded in this card (64,66).

During biosimilar development (in phase I and phase III) clinical experience is limited, therefore it is not possible to identify low-frequency and long-term AEs. Thus, PV is an essential element, as it will allow to compare clinical information, immunogenicity data, PK, and serum concentration of the medicine, as well as aspects related to the quality of the product (64,66).

Annex E represents an example of a biological medicine circuit in the hospital.

7.3. Use of biosimilars and change from the reference biological medicine to a biosimilar, according to the CNFT

In Portugal, the CNFT, an INFARMED, I.P. consulting body, considers that the availability and increasing use of biosimilars improves competition between products, which results in better patient access to biological medicines and contributes to the sustainability of health systems (16).

In Portugal, biologicals are only prescribed in hospitals according to their INN, this allows for a permanent record of medicines, brands, batches, and therapeutic regimens of each patient, guaranteeing adequate control of the process (56).

The treatment should be initiated with the biological or biosimilar that has the lowest cost for the institution that provides it (this is one of the goals to be achieved in all new patients). This must occur in patients with prescriptions from within the institution, and for those coming from external treatment centers –the institutions are responsible for informing prescribers (internal and external) about this objective (56). Cost effective switches should de made whenever possible(56). Each institution should aim to promote change in all clinically stable patients (56).

The process of changing from an RP to a biosimilar or vice versa must safeguard several conditions. For example, presently, for the medicinal products infliximab, etanercept and rituximab, there is sufficient evidence to consider that switching from the reference biological medicinal product to the biosimilar will not lead to a loss of efficacy or an increased risk of AEs (for all indications approved for the corresponding biosimilars) (56). In general, the process must be promoted by the Pharmacy and Therapeutics Commission (CFT) of the hospital institution and, concerning external prescribing centers, by the CFTs of the Regional

Health Administrations, in articulation with prescribers and pharmaceutical services. After the change, the drug must be kept for periods of at least six months in order to ensure its traceability. Everyone involved in the change program (physicians, pharmacists, and nurses) must be informed about the process and its benefits. The decision to change must be explained in detail to the patient by the prescriber. The process must safeguard the time necessary for the physician and the patient to know the conditions of the change. If there is a refusal to change, this decision must be informed to the pharmaceutical services and justified to the local CFT, on a case-by-case basis – until the reason for the refusal is explained, the medication that the patient was already using must remain available. If the above conditions are met, the institution's pharmaceutical services will replace the biological drug with the most appropriate alternative, based on the INN prescription, with the date of the change, brand, and batch of the new drug being recorded. Monitoring and recording of AEs or other events related to the use of the new drug, such as the appearance of signs of immunogenicity, must be maintained (in fact, they should be maintained, but do not require additional monitoring in relation to the reference drug) (16,56,64).

7.4. What a Prescriber Needs to Know

Biosimilars are medicines subjected to high approval standards, so the probability of a problem occurring with any change in the manufacturing process is relatively low. However, healthcare professionals must be aware of the need for greater traceability of these products in the patient's health records. They are not required to be aware of the specific changes that have taken place in the manufacturing process, but they should ensure that the best care is provided and that the medicines are used according to the required conditions, which include using distinctive and product-specific names in health records and being aware of unexpected situations, such as AEs (8). For biosimilars to be prescribed, the medical community must fully understand them. Today, there are several resources to assist the patient in decision-making, such as up-to-date scientific evidence, regulatory requirements, available information on typical questions patients may have regarding treatment and video discussions with clinical experts, among others (54).

Another important aspect that healthcare professionals should consider is the impact of the nocebo effect. This effect is related to patients having negative expectations regarding treatment, which consecutively leads to potentially worse outcomes (67). The nocebo effect is not related to the drug's pharmacology, but to the fact that the patient associates the low cost of the product with its lack of efficacy (68). Improved communication between health professionals and patients, avoiding the use of excessively technical language, can help to

explain that the exchange of a RP for biosimilar is safe and equally effective (69). For example, recently, the European Society of Medical Oncology issued statements to support healthcare professionals in the use of biosimilars in oncology settings (53).

7.5. Patient Needs

Patients often express concern about the efficacy and safety of biosimilars when compared to their RPs. Their low cost is one of the causes, since they fear that health professionals' decision is based only on this fact (4).

Biosimilar availability for patients with arthritis/rheumatism has increased. These patients are, currently, one of the most representative groups using biological medicines. For this reason, EULAR Standing Committee of People with Arthritis/Rheumatism in Europe (SCAPRE) published an article describing what is essential to do to help patients understand biosimilars and therefore make informed decisions. One of the issues addressed in this document is related to the exchange, interchangeability, and replacement of reference biologicals and biosimilars, and it reports the need for clear codes of practice, written in a lay language and developed together with patients. This will ensure that patients can make fully informed decisions about receiving a RP or a biosimilar, assessing the risk/benefit balance and discussing the pros and cons with their medical team (4).

8. Conclusion and Future Perspectives

It is consensual that part of our future involves biotechnology, more specifically biological medicines. Biosimilars are already widely recognized and established in clinical settings and are strong allies in helping people gain greater access to treatments and medicines. As these medicines are much cheaper than the reference biologics, their use guarantees greater financial sustainability for providing health systems. Being a more cost-effective, but identical safety, quality, and efficacy choice, will allow a greater number of patients to benefit from these advanced therapies (36,47).

However, biosimilars present different challenges than generics, especially for manufacturers. The high costs of clinical development are one of the main challenges, as the process of manufacturing a biosimilar requires a high investment and technical capacity. Another obstacle is the existing regulatory differences between the approval of biosimilars and the approval of generics (the regulatory framework for biosimilars is still very recent in most markets). In addition, it is also necessary to gain the trust of health professionals and users, alleviating safety concerns, but for this, it is necessary to invest heavily in marketing

teams (20). The market growth of these drugs requires a constant regulatory and scientific update, forcing companies to innovate (scientific challenge) (1,19,20).

To maximize the earnings from the use of biosimilars, each stakeholder must comply with their responsibilities as efficiently as possible. Physicians should better understand biosimilars to increase their confidence in prescribing them. Both physicians and patients should recognize the potential of nocebo effects and improve communication strategies to limit their impact on clinical outcomes and treatment discontinuation (36,54). Manufacturers must be able to quickly adjust to changes in the market, as well as be efficient enough to minimize costs and be competitively priced keeping product quality, supply sustainability, or PV systems. That is, all stakeholders must collaborate skillfully to achieve the goal of biosimilar development: the focus is to deliver the clinical benefits of biological therapy to patients, contributing to the sustainability of the healthcare system (19,36,54). Therefore, the Pharmaceutical Industry is increasingly investing in new therapies, namely in the development of mAbs fragments, which have the same therapeutic targets as existing mAbs (the molecular weight is lower) (70).

From a regulatory point of view, the focus is on creating a solid and scientifically robust regulatory structure with the capacity of resolving non-consensual points: harmonization of nomenclature, simplification of terminology, extrapolation, interchangeability, and automatic substitution. This will result in less burden for biosimilar companies because the costs of their development are greater (1,2,17).

Although guidelines for the approval of biosimilars have been available for several years, there are still many concepts that need to be addressed to ensure an efficient PV. It is important to note that there are currently no standard requirements for post-approval safety monitoring programs (they vary between manufacturers) (5,14,43). Therefore, these programs are designed through discussions between the manufacturer and regulatory agencies to establish which should be in place. These programs must be covered by mechanisms capable of differentiating AEs resulting from the biosimilar from those resulting from the RP.

Biosimilars naming is not consensual, with the WHO proposing to use a four-letter code ("biological qualifier") for the INN and the FDA indicating that a four-letter suffix should be used. EU MSs indicate that biosimilars must use the same INN as the RP. In fact, the identification of biosimilars is likely to continue to be a challenge until the harmonization of naming conventions takes place (1,5).

The prospects and challenges for biosimilars companies are very much focused on future patent drops. However, now, innovative biological drug companies, in addition to investing in new therapies and products, are also strategically focused on developing biobetters. These

products, despite being considered innovative molecules, have very low development costs and associated risks, since data and studies of previous molecules already exist. As they are innovative molecules, they are entitled to patent and data exclusivity and do not have to wait for the patent on the original medicine to expire. Therefore, they can be marketed maintaining a price equal to that of the RP, or else a higher price is established, as they have superior quality (26,42,71).

The wide variety of challenges associated with biosimilars makes them currently an emerging and strategic field in the context of innovation and development in the pharmaceutical industry, but also a pillar in the sustainability of health systems with an evident and relevant impact on the promotion of public health.

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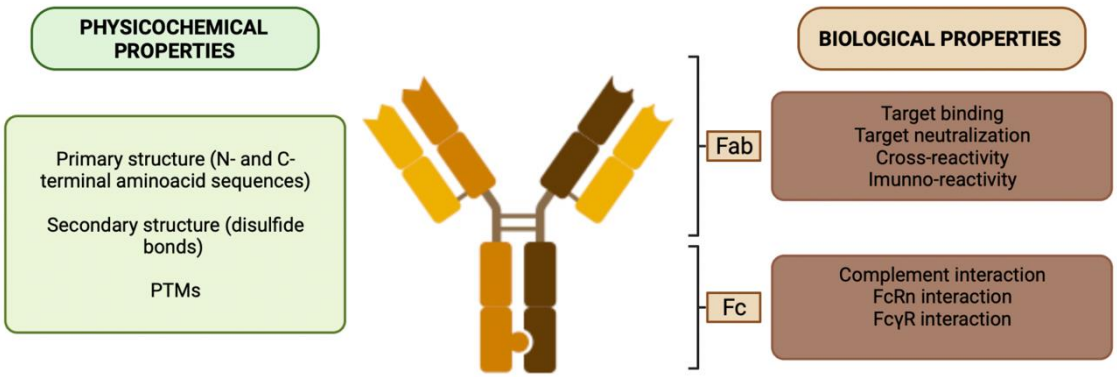
10. Annexes

ANNEX A – Main differences between biosimilars and generics medicines.

	Biosimilars	Generics	Ref.
Product characteristics	Large complex molecules (up to 270000 Da).	Small and simple molecules (up to 300 Da).	(6)
Production	Produced using live organisms - highly sensitive to manufacturing changes. 5-9 years. High production costs.	Produced by chemical synthesis. 2-3 years. Lower production costs.	(6,28)
Structural comparison to reference medication	Highly similar to the RP: same amino acid sequence; but they may differ in minor parts of the structure.	Structurally identical to the reference medicine.	(4,6,14)
Development	Demonstration of biosimilarity using comparability studies between the biosimilar and the RP.	Demonstration of bioequivalence between the generic and the reference medicine.	(4,16,57)
Naming	Each biosimilar has its own brand name: (Same non-brand name as the RP) + (suffix of 4 lower-case letters). E.g.: filgastim.sndz Follow-on insulins are the exception.	Same chemical name (active ingredient) as the reference medicine.	(14,16,17,19,22)
Requirements for approval	Animal and clinical studies (toxicity, PK, PD, and immunogenicity).	No animal or clinical studies are required (only bioequivalence studies). The active ingredient must be identical in strength, dosage form, and route of administration.	(3,6,14,22)
Post-authorization activities	Pharmacovigilance (PV).	Phase IV, risk management plan including PV.	(10,17,43,50,52)
Imunnogenicity	Immunogenic.	Mostly nonimmunogenic.	(17,22,43,50,72)
Equivalence	Data must demonstrate, in each indication, that the biosimilar has no clinically meaningful differences in efficacy and safety.	Each indication approved for the RP can be granted based on demonstrating bioequivalence, without the need for additional clinical data.	(5,14,17,22,52)

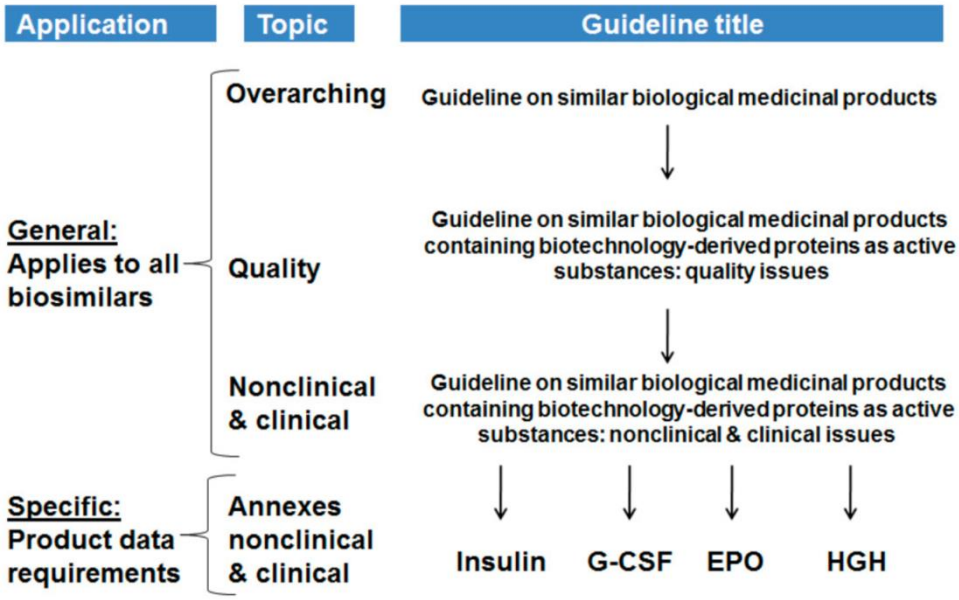
	Confirmatory clinical trials are usually not needed in every indication.		
Interchangeability	Generally, no.	If permitted by state law, pharmacists may automatically substitute the generic for the reference medicine.	(2,17,22,56,72)

ANNEX B – Characterization of a biosimilar mAb, evidencing its physicochemical and biological properties.



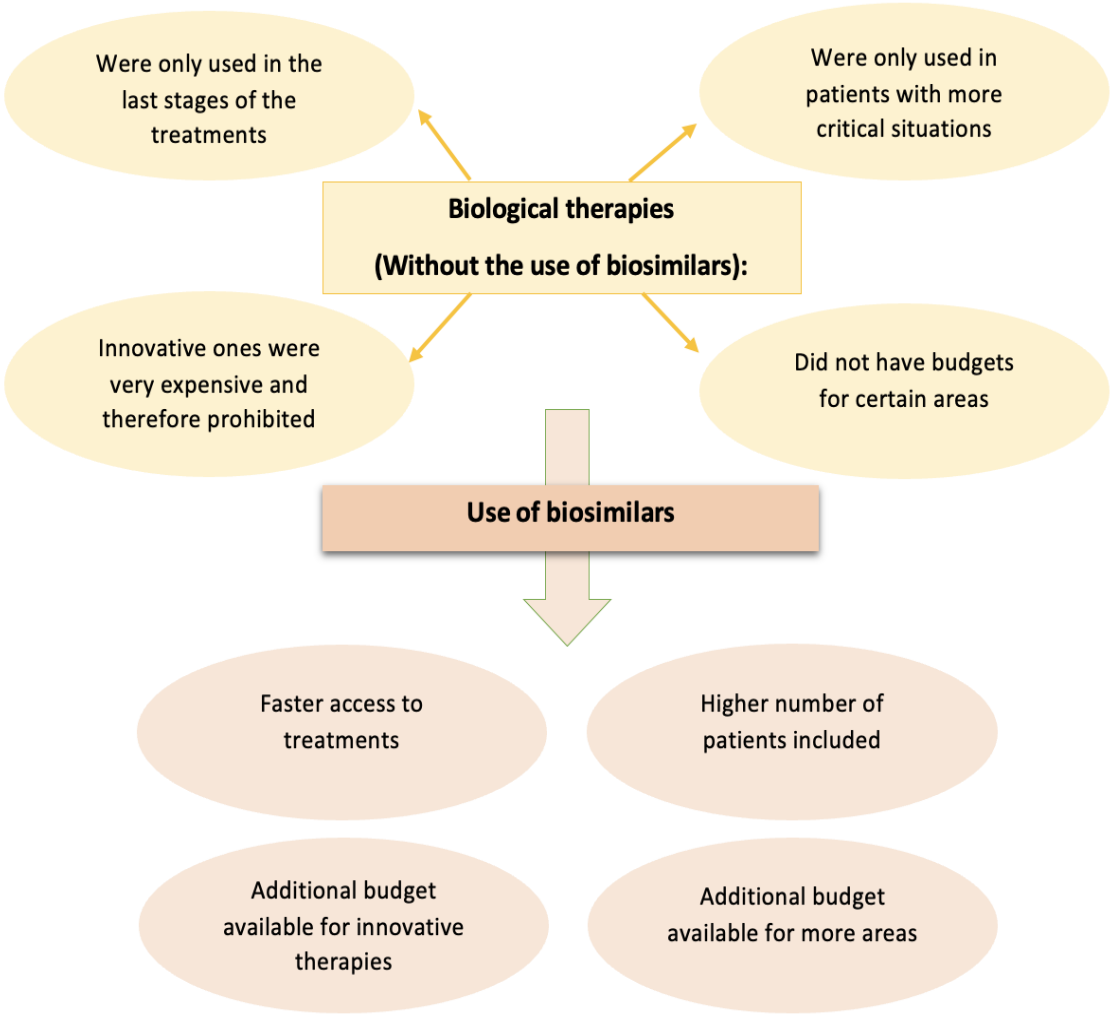
Fab: fragment antigen-binding; Fc: fragment crystallizable; FcRn: neonatal Fc receptor; FcγR: Fc-gamma receptor.

ANNEX C – EMA's regulatory guidelines related to the development and approval of biosimilars (73).



G-CSF, granulocyte colony-stimulating factor; HGH, human growth hormone; INFα, interferon alpha; INFβ, interferon beta; EPO, erythropoietin.

ANNEX D – Main differences in terms of economic savings and public health impact of using biological versus biosimilar medicines.



ANNEX E – Schematic illustration of biological medicine circuit in a hospital context.